

**Neuropsychological assessment in children and adolescent patients
with anorexia nervosa: Exploration and identification of distinct
neuropsychological strengths and weaknesses**

Submitted by Dr Mark Rose to the University of Exeter
as a thesis for the degree of
Doctor of Philosophy in Psychology by Publication
In October 2018

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Abstract

Investigation of the neuropsychological functions associated with anorexia nervosa (AN) may help to better understand this disorder. This thesis aims to explore neuropsychological functioning in children and adolescents with AN using a profiling framework utilising qualitative, case control and cross-sectional designs to identify distinct profiles and their association with clinical characteristics. In addition, a) visuo-processing skills operationalised as central coherence, organisational strategy and visuo-spatial memory and b) planning ability were investigated using case-control design.

Paper 1 reviews neuroscience-based conceptual models of eating disorders which identified a critical volume of empirical studies that allowed integration of theories to preliminarily model relationships between constructs spanning genomics to self-report. Paper 2 describes how neuroscientists and clinicians developed a neuropsychological battery aimed at overcoming identified challenges within the field of AN. Papers 3 and 4 reveal a range of different neuropsychological profiles in children and adolescents with AN rather than one characteristic profile. Paper 5 finds no significant differences between healthy controls and patients with AN in central coherence, organisational strategy and visuo-spatial memory recall, although patients performed significantly better on copy accuracy and took significantly longer to copy. Paper 6 reveals there are no significant deficits in planning found in

young people with AN. There is evidence of subtle differences in learning style and strategy between those with AN and healthy controls.

Findings and their implications for the field of AN are further explored: Developmental trajectory, effects of starvation on neuropsychological functioning, early vs. later AN onset, cognitive remediation therapy as a treatment for AN and future research.

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Statement of original authorship

The work contained in this thesis has not been previously submitted for a degree in any other higher education institution. This thesis contains no material previously published or submitted for publication by another person except where due reference has been made.

Signature:

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Date: 26-09-2018

Dr Mark Rose

Acknowledgements

This thesis by publication would not have been possible without the guidance and support of numerous people. I would like to express my gratitude to the late Professor Bryan Lask, my supervisor at Great Ormond Street Hospital for Children and associate supervisors Dr. Ian Frampton and Dr. Beth Watkins for all of their help and advice since October 2006 when this journey began. Their guidance has been invaluable. Thank you to Professor Huw Williams at the University of Exeter for supervising the final furlong of this journey alongside Dr Ian Frampton.

I would also like to thank the Feeding and Eating Disorders Team at Great Ormond Street Hospital for Children NHS Foundation Trust and The Huntercombe Group for their support and assistance throughout the project.

A special thank you should go to the following Ravello profile collaborators for contributing data: Avon and Wiltshire Mental Health Partnership NHS Trust: Weston General Hospital, CAMHS; Surrey and Borders Partnership NHS Foundation Trust: Frimley Childrens Centre; Cheshire & Wirral Partnership NHS Foundation Trust: CHEDS - Cheshire & Merseyside Eating Disorder Service for Adolescents; Forest Healthcare: Ellern Mede Eating Disorders Service; South West London and St George's Mental Health NHS Trust: Springfield University Hospital; The Huntercombe Group: Huntercombe Hospitals Maidenhead, Stafford & Edinburgh; Child & Family Practice; Oslo Universitetssykehus Ullevål: Regional avdeling

spiseforstyrrelser; Barnesenteret, Oslo Universitetssykehus Aker: Gaustad; Follo BUP, Akershus Universitetssykehus: Røde kors klinikken, Helse Bergen: Haukeland Universitetssykehus; Charite- Universitätsmedizin Berlin: Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Kindes- und Jugendalters; and Universität Basel: Institut für Psychologie

This project has been funded by: The Rosetrees Trust; The Huntercombe Group; Forest Healthcare; Care UK; Goldsmiths University of London; Oslo Universitetssykehus Ullevål: Regional avdeling for spiseforstyrrelser, Norway; and Norwegian Government Health Board, Health South East Norway.

Finally but by no means least, a huge thank you to all of the patients who participated in this study. I am extremely grateful for your patience and time. I truly hope that the findings of this study will be able to benefit sufferers of anorexia nervosa.

Dedications

I would like to dedicate this thesis to my mother, Anne, and late father, Derek. Thank you for the one of the most valuable and life changing lessons you taught me as a child, the importance of education. Thank you.

Chapter 1

Introduction

Anorexia nervosa (AN) is a disorder characterised by refusal to maintain body weight at or above a minimally normal weight for age and height, intense fear of becoming fat even when severely underweight, and distorted body image (American Psychiatric Association, 2013). Individuals with AN often view their personal value as directly related to their weight and shape and deny being underweight even when severely ill. Self-esteem issues, anxiety, depression and obsessional-compulsive (OC) traits are also common to this disorder (Salbach-Andrae et al., 2008). The severe weight loss and malnutrition may lead to a number of serious medical complications including osteoporosis, cardiac abnormalities and even death (Sharp & Freeman, 1993). Mortality rates range from 5.6 to 6.5% (Franko et al., 2013; Sullivan, 1995), although recent estimates are more optimistic, most probably because of improvements in medical stabilisation (Keel & Brown, 2010).

The disorder affects between 0.3 and 2.2% of women in Western countries during their lifetime (Bulik et al., 2006; Hoek & van Hoeken, 2003; Hudson, Hiripi, Pope, & Kessler, 2007; Keski-Rahkonen et al., 2007; Machado, Machado, Goncalves, & Hoek, 2007; Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011; Wade, Bergin, Tiggemann, Bulik, & Fairburn, 2006), occurs more often in females than males (Hoek & van Hoeken, 2003) and peak age of onset is between 15 and 19 years of age (Lucas, Beard, O'Fallon, & Kurland, 1991). Despite typical onset during adolescence, AN can

become a persisting and life-long illness. Keel and Brown (2010) revealed that ten years after initial treatment, only 50% of patients were in remission. Such poor prognosis highlights the need for more engaging and effective treatments for AN. The development of effective approaches is thought to be in part, hindered by a limited understanding of its underlying pathological processes (Kidd & Steinglass, 2012).

There is strong evidence for an interaction between social, psychological, and neurobiological factors in the pathogenesis of AN (Brewerton, Frampton, & Lask, 2009; Nicholls, 2013). However, the precise nature of the neurobiological contribution remains unclear. Studies have revealed anomalies in neuropeptide and neuroendocrine functioning (Bailer & Kaye, 2003), genetic associations (Trace, Baker, Peñas-Lledó, & Bulik, 2013), and changes in brain structure and function (Friederich, Wu, Simon, & Herzog, 2013).

The behavioural and psychological aspects that are commonly associated with AN include obsessionality, rigidity and perfectionism. A particularly challenging concern are the distorted thoughts and beliefs around shape, weight and food and the “thin ideal.” When the disorder is viewed as ego-syntonic, these may act as perpetuating features that potentially underlie the high levels of treatment resistance and relapse rates found in AN (Abbate-Daga, Amianto, Delsedime, De-Bacco, & Fassino, 2013). An approach taken to better understand this complex disorder has been the conceptualisation of the cognitive features seen in AN, in particular neuropsychological

dysfunction. Neuropsychological functioning is conceptualized as the mediator between mental health symptoms including emotional, behavioural, and cognitive functioning and neurobiology (Frampton & Rose, 2013).

Despite numerous reviews indicating anomalies in neuropsychological functioning (e.g., Zakzanis, Campbell, & Polsinelli, 2010), findings from neuropsychological studies have been inconsistent. Criticisms of these studies include the lack of consistency in design (e.g., use of case-control, cross-sectional or longitudinal), small sample sizes, the use of heterogeneous samples both within and between studies and a failure to control for other explanations of neuropsychological impairment (Tchanturia, Campbell, Morris, & Treasure, 2005). This is further compounded by the large variety of available neuropsychological tests which make it difficult to synthesise findings across studies, e.g., Zakzanis et al. (2010) noted that as many as seven different tasks have been used to assess set-shifting and eight for visual-spatial processing style. The heterogeneity of samples may be a result of the stage of illness (acute, weight-restored, long-term remised), length of illness and diagnostic subtype (AN binge/purge and AN-restrictive). Symptomatic variability across studies may also exist depending on whether patients were included according to DSM-III or DSM-IV criteria (Duchesne et al., 2004). There may be a tendency towards publication bias in that a greater volume of research is generally published on neuropsychological functions like set-shifting and central coherence. For example, to date within the adult literature there are two systematic reviews on central coherence (Lang, Lopez, Stahl, Tchanturia, & Treasure, 2014a; Lopez, Tchanturia, Stahl, &

Treasure, 2008) and three on set-shifting (Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007; Westwood, Stahl, Mandy, & Tchanturia, 2016; Wu et al., 2014). However there is only one review on decision-making (Wu et al., 2016) despite evidence of deficits in this particular function noted in early generic reviews (Duchesne et al., 2004; Lena, Fiocco, & Leyenaar, 2004). Furthermore, the vast majority of studies have focused on adults, whilst some have included mixed samples of adolescents and adults. It is inappropriate to conclude that findings based on adults can be applied to children and adolescents in light of evidence of developmental trajectories in neuropsychological functioning across the age span (P. Anderson, 2002; V. Anderson, 2001; V. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001); typical development must be understood before we can conclude on what is 'atypical' (Zelazo & Muller, 2011). Hence, in order to gain a greater understanding of the processes that may underlie the distorted thinking seen in AN and address the challenges and inconsistencies within the field, the neuropsychological performance of young patients with AN has been investigated.

(a) Aims, objectives and results¹

Aims.

The primary aim of this thesis was to explore neuropsychological dysfunction in children and adolescents with AN. A neuropsychological profiling framework was employed in order to identify distinct profiles and their

¹ Headings in this Chapter are those required by Section 2.2.6 of the University of Exeter Teaching Quality Assurance Manual for the presentation of a thesis/dissertation including published papers.

association with specific clinical characteristics, specifically eating disorder symptomatology and weight status, and co-morbidity: anxiety, depression, and OC symptoms.

The second aim of this thesis was to explore two specific domains of neuropsychological functioning in children and adolescents with AN as previous literature on these functions has been lacking in younger persons with AN. Firstly, visuo-processing skills operationalised as central coherence, organisational strategy and visuo-spatial memory with a particular focus on recognition memory. The second assessed domain was planning ability in order to better understand the learning styles and application of strategies used by child and adolescent patients with AN.

Objectives.

In order to investigate the primary aim, four objectives were required to progress from initial problem formulation to the final neuropsychological profiling as follows:

- 1) A systematic literature review of the current conceptual models that endeavour to explain the pathogenesis and maintenance of eating disorders from a neuroscience basis was conducted.
- 2) Given the vast range of neuropsychological tests available, a method of assessing and compiling a battery was required. Neuroscientists attending a Special Interest Group meeting at the Eating Disorders Research Society meeting in Ravello, Italy (2004) set out to develop a global standardised neuropsychological

assessment battery. A working group was established to review the existing neuropsychological literature and make recommendations about suitable tests. A “shortlist” of potential tests was refined through further discussion and feedback at Eating Disorder conferences and other academic and clinical meetings using a “delphic” approach to achieve consensus. This formed the creation of the standardised neuropsychological assessment battery known as the “Ravello Profile”.

- 3) A case series (n=9) piloted the neuropsychological battery.
- 4) Two hundred and fifty three female children and adolescents with AN and 170 healthy controls from 17 collaborating sites completed the neuropsychological battery to identify discrete neuropsychological profiles and their relationship to clinical symptoms. Three stages of data analyses were used: a) Two step cluster analysis, i) hierarchical cluster analysis identified the optimum number of clusters, then ii) *K* means cluster analysis assigned membership to the specified number of clusters. b) Discriminant function analysis to determine which combination of the neuropsychological variables best distinguished the cluster groups and whether these combinations could reliably predict cluster-group membership. c) Between-group analyses with appropriate post-hoc testing, to assess differences in demographic, clinical and neuropsychological variables among cluster groups.

For the secondary aim, two case-control comparison studies determined whether specific neuropsychological inefficiencies consistently identified in adults were also present in a sample of children and adolescent patients with AN as follows:

- 1) For the investigation of the specific domains of central coherence, organisational strategy and visuo-spatial memory in children and adolescents with AN (AN $n=78$, HC $n=78$), a MANOVA model was fitted to explore relationships between the independent variable of group (case vs. control) and the dependent variables of immediate recall, delayed recall and recognition trial from the Rey Complex Figure Task (RCFT: Meyers & Meyers, 1995; Rey, 1941) as well as indexes of central coherence and organisational strategy.
- 2) For the investigation of planning ability in children and adolescents with AN (AN $n=78$, HC $n=78$), performance on the Delis-Kaplan Executive Function System Tower Test (Delis, Kaplan, & Kramer, 2001) was analysed in four stages: a) group differences on achievement, planning and accuracy across *all nine* items, b) group differences on achievement, planning and accuracy on *each* of the nine items and c) multiple regression analyses investigated whether performance on early items, those in which the rules were learned and then applied, predicted performance on later, progressively more difficult items. A multiple regression model was fitted for the whole sample, followed by comparison of multiple regression coefficients per group using Fisher's and Hotelling's t / Steiger's Z tests. d) Correlation between dependent

variables used in (a) with the possible confounders of intelligence and co-morbid depression, anxiety and obsessive-compulsive symptoms.

The studies implemented to investigate the aims were centred on six publications (five empirical peer-reviewed studies and one book chapter) in this thesis. Each paper focused on a specific stage of the research. Taken together, these papers are intended to follow a logical and consistent approach to investigate the aims.

Results.

Chapter 2 (Paper 1): Rose and Frampton (2011). Conceptual Models. In B. Lask and I. Frampton (eds). *Eating Disorders and the Brain*. London: Wiley. 142 – 164.

Seven models were identified and reviewed, the evidence base offered by the original authors was summarised, followed by a brief commentary about the model's *key characteristics, evidence base, clinical applicability and testability*. The seven models were compared on the US Research Domain Criteria (RDoC: US National Institute of Mental Health, 2010) across six neuroscientific constructs: genetic, molecular, cellular, neural circuits, behavioural and self-reports. The main finding was the identification of a critical volume of empirical studies that allowed integration of theories to preliminarily model relationships between the constructs. It is proposed there is a potential role for brain-based mechanisms in the development and/or maintenance of eating disorders. Models have become more comprehensive

over time with some authors considering testability. An identified issue was the different frameworks used within neuroscience that make direct comparison and testability between models difficult, e.g., “neurocircuitry” vs. “behavioural” perspectives.

Chapter 3 (Paper 2): Rose, Davis, Frampton, and Lask (2011). The Ravello Profile: Development of a global standard neuropsychological assessment for young people with anorexia nervosa. *Clinical Child Psychology and Psychiatry*, 16, 195–202. DOI: 10.1177/1359104511401191

Despite an impressive amount of research in the field of AN, several methodological issues make it difficult to generalise results from individual studies. Paper 2 outlined the main issues in this field, specifically that small samples were typically recruited for individual studies due to the rarity of the disorder, and comparison of findings between studies was difficult due to the vast range of neuropsychological tests used. This study described how neuroscientists and clinicians developed a neuropsychological battery aimed at overcoming these challenges.

Chapter 4 (Paper 3): Rose, Frampton, and Lask (2012). A case series investigating distinct neuropsychological profiles in children and adolescents with anorexia nervosa. *European Eating Disorders Review*, 20, 32-38. DOI: 10.1002/erv.1095

Previous research in the field of AN had focused on aggregate group performance, suggesting that the disorder could be characterised by one profile. This case series (n=9, age range 12 years 5 months to 16 years 5 months; BMI range 14.10 to 17.67; BMI age-corrected percentile range 0.01 to 11.93) revealed a range of different neuropsychological profiles in children and adolescents with AN rather than one characteristic profile. Such distinct profiles would be hidden in whole group statistical analyses thus methodology that differentiates between profiles would be required in future studies.

Chapter 5 (Paper 4): Rose, Stedal, Reville, van Noort, Kappel, Frampton, Watkins and Lask (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. *Archives of Clinical Neuropsychology*, 31, 877–895. DOI: 10.1093/arclin/acw068

Three distinct clusters in the AN sample (n= 253; mean age= 15.6, SD= 1.8; median BMI= 15.98 [25th - 75th centile 14.77 – 17.28]; median BMI age-corrected percentile= 2.04 [25th – 75th centile 0.17 – 7.53]) emerged: AN cluster 1 (19%) "neuropsychologically low average to average"; AN cluster 2 (33%) "verbal/visuo spatial discrepancy"; and AN cluster 3 (48%) "verbally strong and neuropsychologically average to high average". Two distinct clusters in age matched healthy controls (n= 170; mean age= 14.50, SD= 2.28; median BMI= 20.80 [25th – 75th centile 18.28 – 22.75]; median BMI age corrected percentile= 63.27, [25th – 75th centile 36.19 – 79.43]) were identified:

HC cluster 1 (48%) demonstrated poor visuo-spatial memory scores and high verbal fluency scores, whilst HC cluster 2 (52%) scored within the average range on all neuropsychological tasks. The distinct profiles provided evidence of neuropsychological heterogeneity in children and adolescents with AN, i.e., there was not one single pattern of weaknesses or specific profile that characterised AN.

Chapter 6 (Paper 5): Rose, Frampton, and Lask (2014). Central coherence, organizational strategy, and visuospatial memory in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 3, 284-296. DOI: 10.1080/21622965.2013.775064

One hundred and fifty-six age-matched participants were included in this study, $n = 78$ children and adolescents with AN and $n = 78$ healthy controls (mean age = 15.2 years, $SD = 1.8$ years; mean BMI for patients = 15.8, $SD = 1.7$; mean BMI age-corrected percentile = 6.5, $SD = 9.5$; mean BMI for controls = 21.9, $SD = 4.1$; mean BMI age-corrected percentile = 61.1, $SD = 28.6$). The MANOVA revealed no significant group differences in the combined dependent variables (immediate recall, recognition trial, and central coherence index), $F(3, 149) = 0.704$, $p = .551$. There were no significant differences between groups in delayed recall ($t = -0.186$, $p = .853$), recognition memory (percentage of local elements recognized- $t = -0.918$, $p = .360$; percentage of global elements recognized- $U = 2,818$, $p = .905$) or organisational strategy (qualitative- $U = 2,623$, $p = .323$; descriptive- $U = 2,844.5$, $p = .761$). When compared with controls, patients with AN scored

significantly higher on accuracy (AN median Copy score= 34 [25th – 75th centile 31 – 36]; HC median Copy score= 31.5 [25th – 75th centile 29.8 – 34]; $U = 2,256.5$, $p = .005$) and took significantly longer (AN median seconds= 156 [25th – 75th centile 122 – 204.3; HC median seconds= 130 [25th – 75th centile 113 – 159.3]; $U = 2,196.5$, $p = .003$) when copying the RCFT. All effect sizes for the dependent variables were small (range, $d = .00$ to $.24$; partial eta squared = $.00$ to $.01$). Given the lower than expected performance of the control group, these findings should be treated with some caution. This study highlighted that in the absence of normative data for neuropsychological functions such as central coherence, we need a deeper, more thorough knowledge of the developmental trajectory and its assessment in young people in the general population before drawing conclusions in AN.

Chapter 7 (Paper 6): Rose, Reville, Iszatt, Levinson, Frampton and Lask (2016). Deconstructing planning ability in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI: 10.1080/21622965.2016.1172312

One hundred and fifty-six age-matched participants were included in this study, $n = 78$ children and adolescents with AN and $n = 78$ healthy controls (mean age = 15.2 years, $SD = 1.8$ years; mean BMI for patients= 15.8, $SD = 1.7$; mean BMI age-corrected percentile= 6.5, $SD = 9.5$; mean BMI for controls= 21.9, $SD = 4.1$; mean BMI age-corrected percentile= 61.1, $SD = 28.6$). Achievement, planning and accuracy were assessed on the Tower Test through a series of multivariate regression analyses. In the examination of

whether performance on early Tower Test Items (3 to 5) predicted performance on later, progressively more difficult Items (6 to 9), multiple regression revealed a non-significant model for the HC group ($R^2 = .030$, $F(3, 72) = .738$, $p = .533$) with no items significantly contributing to the model. There was also a non-significant model for the AN group ($R^2 = .102$, $F(3, 65) = 2.466$, $p = .070$), however Item 5 significantly contributed to this model ($\beta = .307$, $t = 2.496$, $p = .015$). Comparison of the structure of the models was non-significant (direct $R^2 = .030$ and crossed $R^2 = .023$, $Z = .302$, $p > .05$). In contrast to the adult AN literature, no deficits in planning were found in this younger population. There was evidence of subtle differences in learning style and strategy, i.e., faster initiation times in that patients with AN had a significantly faster Mean First Move Time than controls on the orientation and strategy-learning items (Item 1 $U = 1769.5$, $p = .000$; Item 2 $U = 1782$, $p = .000$; Item 3 $U = 1851.5$, $p = .000$; Item 4 $U = 1802.5$, $p = .000$) with corresponding medium effect sizes (r range = .34 to .41) rather than gross planning differences. This may suggest a different default learning style characterised by impulsivity, although this is not at the expense of their overall planning performance.

(b) Research methodology where not otherwise described

The methods for Papers 2 to 5 are described fully in their respective chapters and are summarised in Table 1 below:

Table 1: Summary of research methodology of papers included in this thesis

Chapter/paper	Type- Qualitative or quantitative	Sample size	Design
Chapter 2 (Paper 1): Rose and Frampton (2011)	Qualitative	7 papers	Systematic review of available literature up to 2010
Chapter 3 (Paper 2): Rose, Davis, Frampton, and Lask (2011)	Qualitative	NA	Delphic approach
Chapter 4 (Paper 3): Rose, Frampton, and Lask (2012)	Quantitative	AN n= 9	Case series
Chapter 5 (Paper 4): Rose, Stedal, Reville, van Noort, Kappel, Frampton, Watkins and Lask (2016)	Quantitative	AN n= 253; HC n= 170	Cross-sectional, case-control
Chapter 6 (Paper 5): Rose, Frampton, and Lask (2014)	Quantitative	AN n= 78; HC n= 78	Case-control
Chapter 7 (Paper 6): Rose, Reville, Iszatt, Levinson, Frampton and Lask (2016)	Quantitative	AN n= 78; HC n= 78	Case-control

AN= anorexia nervosa; HC= healthy control

Paper 1 applied a systematic review process to identify conceptual models in AN. Since the methodology was not fully described in the original publication, full details are provided below.

Search Strategy and Information Sources.

A systematic search of published peer reviewed articles up to 2010 was conducted in March 2010 across four databases (Figure 1).

Search terms.

The following search terms were used to search titles, abstracts and key words using population, interventions, comparisons and outcomes (PICO, O'Connor, Green, & Higgins, 2011):

Population: anorexia nervosa AND

Interventions: -

Comparison: -

Outcomes: neuroscience AND model

Eligibility Criteria.

Inclusion criteria were:

Population: Adults or children or adolescents, studies focused on the disorder of anorexia nervosa.

Interventions: Any theoretical or conceptual neuroscience models on the pathogenesis and/or maintenance of anorexia nervosa.

Comparisons: -

Outcomes: Neuroscience-based theoretical or conceptual development within the field of anorexia nervosa.

Study designs: Theory development.

Exclusion criteria were: Studies on a disorder other than anorexia nervosa; studies not reporting a neuroscience-based theoretical or conceptual model of anorexia nervosa; solely animal-based studies; articles that were not in English; the following study designs: randomised controlled trials, cross-sectional surveys, case-control, case study/case series, qualitative studies, cohort studies (historical and classical), ecological studies and reviews.

Data Extraction and Quality Appraisal.

Data extraction focused on the examination of the model's key characteristics, evidence base, clinical applicability and testability. Models were also compared using RDoC (US National Institute of Mental Health,

2010) across six neuroscientific constructs: genetic, molecular, cellular, neural circuits, behavioural and self-reports as a measure of comprehensiveness of content, logical congruence, conceptual clarity and level of abstraction (Fawcett, 1995).

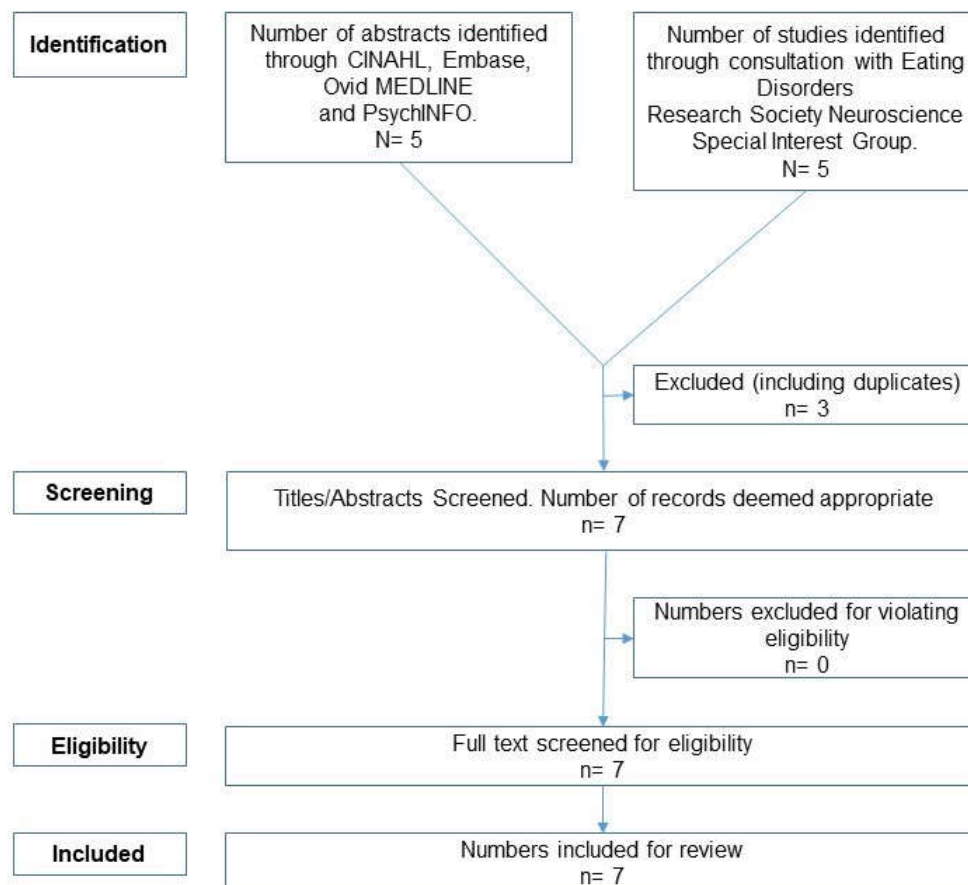


Figure 1. Search strategy, process of identification, screening, eligibility and inclusion for review in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

(c) Contribution made by the papers in the context of the approved field of study

The novel contribution of Paper 1 was the review of conceptual models in eating disorders that has not been conducted before and thus provided an overview of the current state of the science. Furthermore, the seven models were examined under six RDoC neuroscientific constructs- genetic, molecular, cellular, neural circuits, behavioural and self-reports (US National Institute of Mental Health, 2010) thus the evidence base was appraised across the full span of human behaviour. Findings revealed that conceptual models have become more comprehensive over time. Since RDoC provides a common framework for new models to be built on allowing models to be directly compared and tested against each other, this chapter calls for the neuroscientific research community to focus their activity on designing tests to falsify existing models rather than creating more novel ones. Future directions based on an overview of the clinical implications from the seven models were suggested, e.g., psychopharmacological treatments that target specific aspects of the illness such as reducing anxiety, using psychotherapies that focus on a range of psychological aspects, e.g., emotions such as attachment style, cognitive such as enhancing self-efficacy and behavioural such as behaviour repetition, as well as addressing neuropsychological weaknesses with cognitive remediation therapy (CRT). Finally, since this chapter demonstrated the lack of a single comprehensive, causal, explanatory, specific and testable model, the findings informed a neuroscience model (Nunn, Lask, & Frampton, 2011) that accounts for the pathogenesis,

phenomenology and maintenance of AN as well as fulfil the principles of necessity, sufficiency, specificity, empirical derivation and refutability.

The combined outcome of Papers 2 to 4 provided a framework for the investigation of neuropsychological dysfunction in AN, from the creation of a standardised test battery to identification of distinct neuropsychological profiles. Papers 2 and 3 provided clinicians and researchers with a standardised neuropsychological test battery that specifically targeted impairments that have mostly been shown to be dysfunctional. This paved the way for an international, multi-site collaboration who committed to using the “Ravello Profile” neuropsychological battery with children and adolescents with AN as well as integrating data in a shared database. This was an initiative that had not been undertaken before in the field of eating disorders. Paper 3 was a pilot study that demonstrated AN in those under 18 years of age could be characterised by more than one neuropsychological profile. Paper 4 extended the methodology and identified a range of profiles in children and adolescents with AN. Paper 4 was unique in that it was the first to conduct neuropsychological profiling using a neuropsychological battery in a large cohort of children and young people with AN. The main findings were that distinct neuropsychological profiles exist in young people with AN and that neuropsychological differences between individuals with AN and HCs were relatively subtle. This study also highlighted the importance of comparing with an HC sample to identify the clinically meaningful neuropsychological patterns of responding. Neuropsychological profiling may both inform research, e.g., the association of profiles to factors such as outcome, risk factors, and illness trajectories, and have clinical benefits

through its potential to predict longer term prognosis, inform individually tailored treatment strategies and offer insight into the underlying neurobiology of AN.

Papers 5 and 6 were a response to the scarcity of neuropsychological studies in children and adolescents with AN. Visuo-spatial processing and planning impairments found in adults were not replicated in younger patients. These findings challenge the adult-oriented assumption that restricted eating is a *consequence* of concerns about weight and shape. Papers 5 and 6 outline investigations of whether identified impairments in adults with AN were also present in younger patients aged between 10 and 18 years. Paper 5 was the first study to report performance data on central coherence in young healthy controls and patients with AN. Contrary to evidence from adult-based AN research, this study revealed a lack of significant differences in the domains of visuospatial memory, central coherence, and organization strategy. This study also highlighted that a thorough knowledge of the developmental trajectory and its assessment in young people in the general population was required before drawing conclusions about these functions in young patient populations. Paper 6 revealed evidence of subtle planning differences characterised by faster initiation times. The clinical implication of Paper 6 draws attention to the expectations clinicians may hold about novel therapies such as CRT and its application in young populations, i.e. those under 18 years of age. Specially, whether anticipated change and performance are in line with what might be expected in terms of a) evidence of subtle inefficiencies vs. gross impairments, for example compared to the

adult literature on planning (e.g., Zakzanis et al., 2010), this study does not support the existence of a gross planning impairment in young patients with AN as the mean scaled score on the Tower Task in the AN group was in the average range; b) developmental trajectory in that studies using tower tests report an improvement in planning throughout childhood and adolescence (e.g., Luciana, Collins, Olson, & Schissel, 2009) and c) whether performance in one domain is mediated by performance in another. Luciana et al. (2009) highlight that the interpretation of improved planning times with age is complex as this is associated with increased inhibitory control and a maturing speed-accuracy trade-off.

Chapter 8: Conclusion and recommendations provides a) critical appraisal of Papers 1 to 6, b) comparison of Papers 1 to 6 to relevant adult as well as child and adolescent neuropsychological literature in AN, c) considerations for the field of AN (developmental trajectory, effects of starvation on neuropsychological functioning and early vs. later AN onset), d) treatment in AN with a focus on CRT, and e) clinical and research implications.

(d) Statement of the candidate's contribution to co-authored papers

A Vancouver Declaration is appended for each co-authored paper to clarify the contribution of other authors. My contribution to each paper were as follows:

Chapter 1: I wrote this chapter.

Chapter 2 (Paper 1): Led on conception, design, writing and compilation of manuscript, established methodology, data analysis, preparation of tables and led on revisions in response to co-author comments.

Chapter 3 (Paper 2): Led on writing and compilation of manuscript, data analysis, preparation of tables, submitted paper and led on revisions in response to editorial comments.

Chapter 4 (Paper 3): Led on conception, design, writing and compilation of manuscript, established methodology, data analysis, preparation of tables and figures, submitted paper and led on revisions in response to editorial comments.

Chapter 5 (Paper 4): Led on conception, design, writing and compilation of manuscript, established methodology, data analysis, preparation of tables and figures, submitted paper and led on revisions in response to editorial comments.

Chapter 6 (Paper 5): Led on conception, design, writing and compilation of manuscript, established methodology, data analysis, preparation of tables and figures, submitted paper and led on revisions in response to editorial comments.

Chapter 7 (Paper 6): Led on conception, design, writing and compilation of manuscript, established methodology, data analysis,

preparation of tables and figures, submitted paper and led on revisions in response to editorial comments.

Chapter 8: I wrote this chapter.

(e) Literature review

Chapter 2 (Paper 1) contains a systematic literature review of the current conceptual models of the pathogenesis and maintenance of eating disorders from a neuroscience perspective.

Chapter 2

Paper 1: Conceptual models

Mark Rose¹ and Ian Frampton²

¹ *National Research Coordinator, Huntercombe Group, UK*

² *Great Ormond Street Hospital for Children, London, UK*

Rose, M. & Frampton, I (2011). Conceptual Models. In Lask, B., & Frampton, I. (2011). *Eating Disorders and the Brain*. Chichester: Wiley-Blackwell.

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Chapter 3

Paper 2: The Ravello Profile – Development of a global standard neuropsychological assessment for young people with anorexia nervosa

Mark Rose^{1,2}, Jennifer Davis¹, Ian Frampton^{2,3} & Bryan Lask^{1,2,3,4}

¹ *The Huntercombe Group, UK*

² *Department of Child and Adolescent Mental Health, Gt. Ormond St. Hospital for Children NHS Trust, London, UK*

³ *Division of Psychiatry, Oslo University Hospital, Norway*

⁴ *Ellern Mede Centre, London, UK*

Rose, M., Davis, J., Frampton, I., & Lask, B. (2011). The Ravello Profile - development of a global standard neuropsychological assessment for young people with anorexia nervosa. *Clinical Psychology and Psychiatry*, 16(2), 195-202. DOI: 10.1177/1359104511401191

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Chapter 4

Paper 3: A case series investigating distinct neuropsychological profiles in children and adolescents with anorexia nervosa

Mark Rose^{1,2}, Ian Frampton^{2,3} & Bryan Lask^{1,2,3,4}

¹ *The Huntercombe Group, UK*

² *Feeding and Eating Disorders Service, Department of Child and Adolescent Mental Health, Gt. Ormond St. Hospital for Children NHS Trust, London, UK*

³ *Regional Eating Disorders Service, Division of Psychiatry, Oslo University Hospital, Norway*

⁴ *Ellern Mede Centre, London, UK*

Rose, M., Frampton, I., & Lask, B. (2012). A Case Series Investigating Distinct Neuropsychological Profiles in Children and Adolescents with Anorexia Nervosa. *European Eating Disorders Review*, 20(1), 32-38. DOI: 10.1002/erv.1095

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Chapter 5

Paper 4: Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses

Mark Rose^{1,2}, Kristin Stedal³, Marie-Claire Reville^{1,5}, Betteke Maria van Noort⁶, Viola Kappel⁶, Ian Frampton^{1,3,5}, Beth Watkins¹ & Bryan Lask^{1,3,4,5}

¹ *Feeding and Eating Disorders Service, Department of Child and Adolescent Mental Health, Great Ormond Street Hospital for Children NHS Foundation Trust, UK*

² *The Huntercombe Group, UK*

³ *Regional Eating Disorders Service, Oslo University Hospital, Norway*

⁴ *Rhodes Farm Clinic, Care UK, UK*

⁵ *College of Life and Environmental Sciences, University of Exeter, UK*

⁶ *Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Charite- Universitätsmedizin Berlin, Germany*

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses.

Archives of Clinical Neuropsychology, 31(8), 877–895. DOI:

10.1093/arclin/acw068

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Chapter 6

Paper 5: Central coherence, organisational strategy and visuo-spatial memory in children and adolescents with anorexia nervosa

Mark Rose^{1,2}, Ian Frampton^{1,3,5} & Bryan Lask^{1,3,4}

¹ *Feeding and Eating Disorders Service, Department of Child and Adolescent Mental Health, Great Ormond Street Hospital for Children NHS Foundation Trust, UK*

² *The Huntercombe Group, UK*

³ *Regional Eating Disorders Service, Oslo University Hospital, Norway*

⁴ *Care UK, UK*

⁵ *College of Life and Environmental Sciences, University of Exeter, UK*

Rose, M., Frampton, I., & Lask, B. (2014). Central Coherence, Organisational Strategy and Visuo-Spatial Memory in Children and Adolescents with Anorexia Nervosa. *Applied Neuropsychology: Child*, 3(4), 284-96. DOI: 10.1080/21622965.2013.775064

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Chapter 7

Paper 6: Deconstructing planning ability in children and adolescents with anorexia nervosa

Mark Rose^{1,2}, Marie-Claire Reville^{2,5}, Amber Iszatt⁵, Simon Levinson⁴, Ian Frampton^{2,3,5} & Bryan Lask^{2,3,5,6}

¹ *The Huntercombe Group, UK*

² *Great Ormond Street Hospital for Children NHS Foundation Trust, UK*

³ *Regional Eating Disorders Service, Oslo University Hospital, Norway*

⁴ *Ellern Mede Eating Disorders Service, UK*

⁵ *College of Life and Environmental Sciences, University of Exeter, UK*

⁶ *Care UK, UK*

Rose, M., Reville, MC., Iszatt, A., Levinson, S., Frampton, I. and Lask, B. (2016). Deconstructing planning ability in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI: 10.1080/21622965.2016.1172312

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Chapter 8

Discussion and recommendations

In this chapter I shall provide a critical appraisal of the thesis papers via application of quality appraisal tools used in research, followed by an overview of the most recent developments in neuropsychology in the field of AN, and finally implications and future directions for clinicians and researchers to consider.

Critical appraisal

It is important to systematically examine the reliability and validity of any research in order to ascertain whether it makes a valid contribution. In order to minimise subjectivity in evaluating my own work, the papers within this thesis were critically appraised using one of three tools. Appraisal tools were chosen based on their methodological specificity, i.e., their ability to appraise specific research designs. Paper 1 was appraised using the Critical Appraisal Skills Programme (CASP) checklist for systematic reviews (Critical Appraisal Skills Programme, 2018a) which consisted of ten items. Question 5 was dropped as it was not applicable since it asked about combining quantitative data. Question 7 referred to precision of results. For the purposes of this appraisal this item was expanded to include comprehensiveness, congruence and clarity of the theoretical concepts.

Paper 2 was a methods development piece which reported on a qualitative process. Although this paper was not strictly a qualitative article, the CASP checklist for qualitative research (Critical Appraisal Skills Programme, 2018b) was used as an appraisal tool. Question 7 referred to ethical considerations. For this paper, the question was considered irrelevant as ethical approval was not sought since the study did not use patient data. A total of nine items were used.

Paper 3 was appraised using the Quality Assessment Checklist for case studies/series (Moga, Guo, Schopflocher, & Harstall, 2012). This tool has 18 items, however four were dropped as they were considered irrelevant- Q8- additional interventions, Q11- measurement of outcomes pre and post intervention, Q13- length of follow-up reported, and Q14- loss to follow-up reported. Thus 14 items were used.

Papers 4 to 6 were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology tool (STROBE, Vandenbroucke et al., 2007). The STROBE consists of a checklist of 22 items to ensure the quality of reporting of observational studies. This tool was chosen as it covered cohort, case-control and cross-sectional survey research designs. Some items were adapted, specifically, the original terms “outcomes” and “exposures” were replaced with “dependent variables” and “independent variables”. See appendix 1 for full details for each appraisal. A quality score was calculated for each paper as a percentage of the total number of criteria met.

In terms of general considerations of the quality of the included studies, the different methodologies spanned the hierarchy of evidence (Figure 2 below). A case series has a low position in the hierarchy of evidence and is considered the weakest study design from which to obtain empirical evidence, thus derived results are generally ranked as low quality. Next are the observational, quantitative studies, using case-control and cross-sectional survey design. These are considered stronger than case series designs, although they are not as strong as randomised controlled trials.

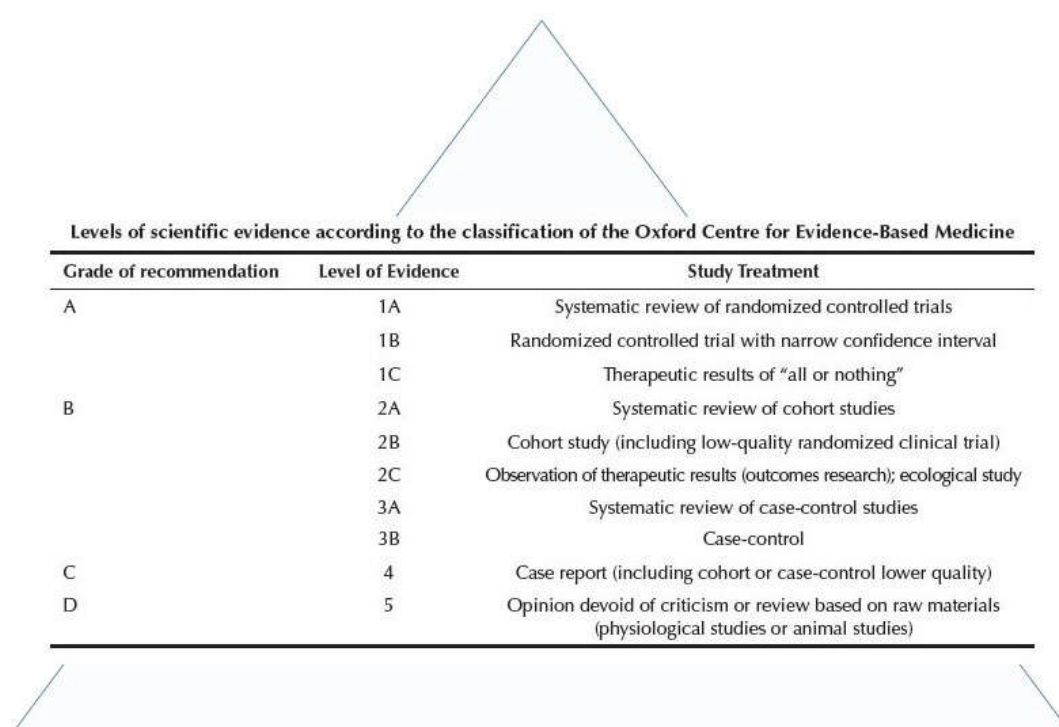


Figure 2. Hierarchy of evidence. Studies placed in a superior localisation of the hierarchy show greater power of evidence. Adapted from Centre for Evidence-Based Medicine (2009).

Table 2: Quality appraisal criteria met for Papers 1 to 6.

Chapter/paper	Quality appraisal tool	Criteria met (Percentage)
Chapter 2 (Paper 1): Rose and Frampton (2011)	CASP checklist for systematic reviews	9/9 (100%)
Chapter 3 (Paper 2): Rose, Davis, Frampton, and Lask (2011)	CASP checklist for qualitative research	4/9 (44%)
Chapter 4 (Paper 3): Rose, Frampton, and Lask (2012)	Quality Assessment Checklist for case studies/series	9/14 (64%)
Chapter 5 (Paper 4): Rose, Stedal, Reville, van Noort, Kappel, Frampton, Watkins and Lask (2016)	STROBE	16/22 (73%)
Chapter 6 (Paper 5): Rose, Frampton, and Lask (2014)	STROBE	17/22 (77%)
Chapter 7 (Paper 6): Rose, Reville, Iszatt, Levinson, Frampton and Lask (2016)	STROBE	17/22 (77%)

CASP: Critical Appraisal Skills Programme; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Table 2 shows the quality appraisal criteria met for each paper. Overall, there were no major failings; however flaws were identified in all of the papers. Paper 1 met the nine criteria set out in the appraisal tool. However, a flaw that was not identified by the appraisal tool was the lack of reported methodology since this paper was published as a non-peer reviewed book chapter; had this been published in a journal then methodology would have been required. This was considered a flaw as there is no way for readers to replicate the review or assess appropriateness of databases searched, search terms or inclusion/exclusion criteria.

Paper 2 was a methods development piece which reported how the battery was developed. This may account for why only a moderate score was

achieved in its critical appraisal. Specific weaknesses were not clarifying the aims of the study and not reporting the procedure or data analysis used in the Delphi process. The Delphi technique is an efficient way to collect information from a group of knowledgeable people (i.e. a panel) by taking into consideration the opinion of each member on the panel. There are usually four core features: 1) response anonymity (it allows a sharing of responsibility and releases responders' inhibitions), 2) iteration (processes occur in rounds) and 3) controlled feedback (showing the distribution of the panel's response), and 4) statistical aggregation of panel responses (expressing judgment using summary measures of the full group response). The strength of this paper would have been considerable improved had the aims, method and data analysis been reported.

Paper 3, the case series, the inclusion criteria lacked clarity. Cases were chosen due to their distinctive neuropsychological profile to illustrate a range of profiles, yet specific, distinguishing neuropsychological features were not specified. Furthermore, it is not explicitly stated a priori that patients must meet a specific diagnosis, age or gender. Cases were not recruited consecutively, which may make the overall findings subject to bias. The representativeness of the sample was raised in the discussion though, "This raises the question of whether they are outliers or whether they are representatives of actual unique clusters of performance." (p. 69). No statistics were reported, the results were descriptive. Statistical comparison of the profiles to the population mean would have determined whether performance was impaired relative to the general population. When

considering whether participants entered the study at a similar point in the disease, all participants were ill at the time of recruitment. Weight status was low relative for their age (all below the 12th percentile). However, severity of symptoms varied from low to high (Global EDE range 0.76 to 5.70) suggesting a degree of heterogeneity of the clinical sample. The non-reporting of adverse events could be interpreted as a weakness. However, this item may be irrelevant to this study as neither the assessment was non-invasive nor did it use any drugs. Finally, no details on funding or conflicts of interest were provided.

For Papers 4 to 6, the same set of flaws were consistently identified. Firstly, the study design was not apparent from the title. Whilst this may be important for epidemiological studies, this information may not adversely affect the quality of the studies in this thesis since study design was apparent from the abstract. Secondly, in terms of main results, whilst Paper 4 reported the percentages of missing data for the independent variables (neuropsychological tests) and how these were handled, Paper 5 and 6 did not. Missing data were apparent in these studies from inspection of the tables. Even though missing data were acknowledged in Paper 4, the lack of a sensitivity analysis means we cannot be certain of its impact on the findings of the study. The same applies to Papers 5 and 6. The third issue concerns potential confounders. Different methods of identification and control were employed across the studies. For Paper 4, whilst overall IQ did not differ between groups, Matrix Reasoning was significantly higher in the AN compared to HC group (small to medium effect size). However, this measure

of visual processing was not controlled for in any of the analyses. Paper 5 did not address the issue of potential confounders, despite obvious sample characteristic differences between the groups. Paper 6 specified, a priori, intelligence and co-morbid depression, anxiety and OC symptoms as potential confounders. These were correlated to the dependent variables from the Stage One analysis (Total Achievement Score, Mean First Move Time (seconds), Time-per-Move Ratio, Move Accuracy Ratio, Total Errors and Errors-per-Item Ratio). Significant correlations were found in the healthy control groups between Total Errors and Error-per-Item Ratio and the three co-morbidities. Since they were of a small effect size, these were not controlled for. A potential flaw here is that this should have been empirically tested using a sensitivity analysis. For Papers 5 and 6, funding information was not provided.

Although generalisability was not a major flaw across the papers, a degree of caution must be taken with Paper 4 as identified by Q21. Epidemiological studies suggest peak age of onset is between 15 and 19 years of age (Lucas et al., 1991), thus the findings are generalisable to the clinical population given the age range in the sample. Furthermore, the large number of collaborator sites ensured the clinical sample was both heterogeneous, yet from a fundamental clinically similar eating disordered population (since all participants were clinically diagnosed with a restrictive-type eating disorder). Thus the sample is likely to be more representative of the young AN population (i.e. <19 years of age) as a whole than studies based on smaller numbers from one or two clinics. On the other hand,

findings may not be generalisable to those outside the age range of this study (< 9 and > 19 years old). Similarly, Papers 5 and 6 focused on those under 19 years of age, thus findings may not be generalisable to later-onset AN. Findings from Papers 4 to 6 may not be generalisable to those with no or low levels of co-morbid depression, anxiety and OC symptoms.

Finally, a weakness across Papers 2, 3 and 4 was the reliance of inspecting reviews at the time to inform which neuropsychological tasks to include in the Ravello Profile. An additional and arguably stronger approach would have been to use a theoretical executive functioning framework, for example Miyake et al. (2000) proposed a three factor model consisting of shifting, inhibition and updating (i.e. working memory). The lack of a working memory task limits the Ravello Profiles ability to elucidate on the role of executive functions in AN.

Comparison to the relevant literature

Theoretical models of AN.

Since the publication of Paper 1, two further theoretical models have emerged. Chen, Papies, and Barsalou (2016) bring together research on the neural responses of eating and food cues in healthy individuals as well as across the eating disorder spectrum. Building upon the neural model proposed by Kaye, Fudge, and Paulus (2009) and integrating a series of systematic reviews on the neurobiology of eating behaviours and eating disorders, Chen and colleague propose the “core eating network”. The model outlines a dorsal control pathway and a ventral reward pathway in the brain

that modulate food consumption. Imbalance between these two networks manifest as impairment in executive functions ranging from over-controlled/rigidity (i.e., low reward, high inhibition) to under-controlled/disinhibited (i.e., high reward, low inhibition). The authors describe how this neatly maps onto the spectrum of eating and weight disorders, in that individuals with AN are characterised by over-controlled tendencies whereas individuals with binge-eating disorder or overweight/obesity present with under-controlled tendencies.

Walsh (2013) proposed that the persistence of AN can be conceptualised as a well-ingrained maladaptive habit. Early developmental and psychosocial factors may set the scene for weight loss to occur, i.e., dieting becomes a goal-directed action that is highly rewarding (action outcome learning). Neural networks in the amygdala, the ventral striatum and the orbitofrontal cortex are proposed to play a key role in this early stage as dieting behaviour is recognised and “coded” as rewarding. Over time, the characteristic dieting behaviours themselves become intensely rewarding as they are engaged in persistently and repeatedly. This has the effect of “overtraining” and producing a habitual response (stimulus-response learning). The dorsal striatum and the dorsolateral prefrontal cortex are proposed to play a more critical role in this later stage. This in turn interacts with emotional factors, for example dieting being associated with modulating emotional distress, i.e., the relief of negative affect due to dieting.

Adult neuropsychological literature in AN.

Eleven systematic reviews have appraised adult neuropsychological research in AN, four of which have been broad in scope. Duchesne et al. (2004) revealed a general consensus of deficits found in attention, visuo-spatial and visuo-construction. In terms of executive functioning, some patients showed impairments in the domains of planning, problem solving and flexibility. Lena et al. (2004) found supporting evidence of either deficits or at least poorer performance relative to healthy controls in executive functions/abstract reasoning, visuo-spatial ability, attention/vigilance, verbal functioning and memory. Mixed findings were found for learning. Similarly, Zakzanis et al. (2010) have shown a general consensus of poorer performance in problem solving, decision making and inhibition (small to medium effect sizes). Set-shifting differences were in the small to medium effect size range, and note that previous research "...may have overemphasized the reliability of set-shifting impairments in patients with AN..." (p.101). The authors also draw attention to the modality of the task, i.e., visual/perceptual vs. verbal, in that performance tends to be worse on visual or perceptual based set-shifting tasks. With regard to visuo-spatial skills (processing and memory), the authors conclude that this domain may be impaired in patients with AN (effect sizes approaching the medium to large range). Such difficulties may go towards explaining the distorted body image often reported in those with AN. Verbal skills were found to have only a very small effect size, whilst verbal memory was considered impaired in AN (effect sizes in the small to medium range). A moderate impairment was also found for processing speed (medium effect size). Jáuregui-Lobera (2013) reported evidence of attentional bias to eating disorder related stimuli (such as "fat"

and “thin” words) and attentional disengagement to food related visual stimuli, faster motor speed in terms of drawing and copying tasks, poorer ability in verbal memory alongside a memory bias for anorexia related words, visuo-spatial deficits, and difficulties in abstraction, flexible thinking and poorer decision making capacity in those with AN.

Seven reviews have focused on specific domains- central coherence (Lang et al., 2014a; Lopez et al., 2008), set-shifting (Roberts et al., 2007; Westwood et al., 2016; Wu et al., 2014) selective attention (Dobson & Dozois, 2004; Johansson, Ghaderi, & Andersson, 2005) and decision-making (Wu et al., 2016). For central coherence, findings indicate that patients with AN show a preference for local processing at the expense of global processing and tend to have difficulties in identifying simple shapes embedded within a background as well as replicating and recalling fewer details from complex visual designs. Lopez et al. (2008) concluded from their meta-analysis that there were clear global processing deficits across the eating disorder spectrum, and some weaker evidence suggesting superiority in local processing. However, they acknowledged that not all of the studies they reviewed set out to look at central coherence directly, and that some of the tasks used also made demands on aspects of executive function or attention. In terms of set-shifting, impaired performance is often characterised by excessive or preservative errors. Roberts et al. (2007) found that the majority of the 15 set-shifting studies in the meta-analysis showed poorer performance in the AN group compared to healthy controls (small to large effect sizes) that spanned a range of illness states and most of the six set-shifting tasks used.

They noted that, from limited data, it appeared that the deficit remained after weight restoration in AN. Roberts et al. note that there appeared to be a difference in the sensitivity of the measures used. Specifically the Haptic Illusion Task, a tactile perceptual task, was associated with the large effect sizes, whilst the TMT was associated with small to medium effects. The authors also note that set-shifting difficulties were found in a number of psychiatric conditions, as noted from a search of other reviews in the set-shifting domain. This suggests that set-shifting difficulties could be an endophenotype that broadly increases the risk of developing/maintaining a range of psychiatric disorders. Regarding selective attention, Dobson and Dozois (2004) showed selective attentional biases on the Stroop task (Stroop, 1935) were specific to body/weight stimuli (moderate effect size) whilst food and classic Stroop effects were minimal. The authors proposed a specific attentional bias, in that patients with AN may be more vigilant to body or shape stimuli than to food-related stimuli. Body related stimuli may represent the object to be avoided and thus represent the greater psychological threat. However, it should be noted that all three comparisons in the meta-analysis (body/weight, food, and classic Stroop) failed the test of homogeneity, suggesting that the existing effect size estimates were not reliable. Finally, support exists for altered reward-related decision-making in adults with AN (Wu et al., 2016). Findings suggest that in decision-making tasks, patients with AN have difficulty in learning the optimal response to maximize a long-term reward over less valuable but more immediate short-term rewards. Such findings have been linked to either an inability in incorporating reward based

feedback, or that those with AN have a different qualitative experience in response to rewards compared to healthy controls.

Child and adolescent neuropsychological literature in AN.

The child and adolescent literature is comparatively lacking. For example, only four out of 14 (Lena et al., 2004) and 18 out of 71 (Reville, O'Connor, & Frampton, 2016) reviewed studies focused on younger people with AN. Systematic reviews based on younger people with AN have been conducted in three domains: set-shifting, central coherence and decision-making. Two reviews on set-shifting in young people with AN suggest evidence of weaknesses that were either less pronounced than those found in adults with AN (Lang, Stahl, Espie, Treasure, & Tchanturia, 2014b) or of equal severity (Wu et al., 2014). However, Westwood et al. (2016) concluded from a meta-analysis of four studies that overall there were no significant differences in set-shifting between child and adolescents with AN and HCs. Regarding central coherence, Lang and Tchanturia (2014c) report evidence of inefficient global processing in children. However, this should be taken with caution as the conclusion was partly based on visual comparison of AN mean central coherence index scores from two studies (Dahlgren, Lask, Landrø, & Ro, 2013; Rose et al., 2012) to HCs mean performance from another study (Tenconi et al., 2010) rather than a statistical aggregate comparison. In terms of decision-making, Wu et al. (2016) reported a lack of supportive evidence for disadvantageous reward-related decision-making in children and adolescents with AN.

Findings of this thesis vs. the known literature.

With regards to the specific findings of the papers in this thesis, there was mixed support for the above reviews. Regarding visuo-spatial memory, when the data analysis procedure allowed for differentiation of neurocognitive profiles, Paper 4 supported the generally held view of weak to impaired performance in visuo-spatial memory in those with AN in that two AN clusters demonstrated weak performance (Paper 4: AN clusters 1 and 2). However, comparison of *overall* group means (Paper 4 and Paper 5) indicated that visuo-spatial memory did not significantly differ compared to age-matched HCs, highlighting that analyses of aggregate group performance can mask subtle differences.

Support for central coherence inefficiencies in young people with AN has mixed support from this thesis. On the one hand central coherence performance was generally weaker in HCs, i.e., controls generally started the copy trial with less global elements, copied key global elements in a fragmented fashion and demonstrated a more local processing copy style compared to those with AN (Paper 4). Across the three AN clusters, Z scores were all within one standard deviation of the population mean. Paper 5 did not find significant differences between young cases with AN and aged-matched HCs on central coherence or organisational strategy. These findings could be interpreted as not supporting the Lang and Tchanturia (2014c) review of inefficient global processing in children and adolescents with AN. On the other hand, the discriminant function analysis determined the strongest distinguishing characteristic for cluster membership was visuo-spatial

processing which was based on both immediate and delayed recall trials and central coherence (Paper 4). As previously noted, Lang and Tchanturia (2014c) draw their conclusion of inefficient global processing in children with AN from visual comparison of central coherence index mean scores between case and control groups from different studies that were not matched which arguably confounds their conclusion. The finding from Paper 4's discriminant function analysis was that *visuo-spatial processing* was the strongest distinguishing feature, i.e., this encompassed both central coherence as well as memory recall (short and long term) thus it was the combination of these processes which contributed to the distinction, not solely central coherence.

Relative to normative data, executive functions (cognitive flexibility, inhibition and planning) were in the average to high average range (Paper 3) whilst in Paper 4 it was demonstrated that performance was in the average range across all three AN clusters. Overall group mean Z scores (i.e. AN n= 253, HC n= 170) in Paper 4 showed cognitive flexibility performance was mixed, in that verbal flexibility (both total and accuracy) performance was significantly higher in those with AN, whereas the TMT revealed significantly poorer performance in those with AN compared to HCs. Performance on the Brixton Task did not significantly differ between children and adolescents with AN and HCs. However, it should be noted though that whilst significant differences between overall group means emerged in tasks of cognitive flexibility, differences in absolute scores were all within ± 1.23 SD of the norm (i.e., Z score of zero) and corresponding effect sizes were all in the small range. Thus these data do not indicate "impaired" functioning of cognitive

flexibility in children and adolescents with AN and is in line with reviews of set-shifting in younger populations which appear to find a lack of evidence of impaired set-shifting in those with AN compared to HCs (Lang et al., 2014b; Westwood et al., 2016). Furthermore, the discriminant function analysis revealed verbal flexibility as a distinguishing characteristic of cluster membership, yet intriguingly the TMT did not despite it showing significant post-hoc differences between AN and HC clusters. This may be in line with reported modality differences of cognitive flexibility tasks (Roberts et al., 2007; Zakzanis et al., 2010). Whereas in the adult literature there are generally reports of poorer performance in those with AN compared to HCs (e.g., Roberts et al. (2007) review based on the TMT, Wisconsin Card Sort Test, Brixton task, Haptic Illusion, CatBat task and the set-shifting subset of the Cambridge Neuropsychological Test Automated Battery), the distinguishing cognitive flexibility feature in younger AN populations was their relatively stronger verbal flexibility compared to HCs.

Inhibition did not significantly differ in overall group mean Z scores, yet cluster-wise AN cluster 1 revealed significantly weaker performance on Colour-Word Interference condition 3 compared to the other two AN clusters and two HC clusters (Paper 4). Dobson and Dozois (2004) note from the adult literature that attentional biases are most marked when using body or weight related stimuli instead of the classic Stroop stimuli. The Colour-Word Interference task used in the D-KEFS used classic Stroop stimuli which might account for the lack of significant differences found between AN and HC overall group means.

Those with AN did not show poorer performance in planning compared to controls; performance in both groups was within the average normative range (Paper 4). The Tower Task was the only task to not show any significant post-hoc differences between AN-HC clusters and did not emerge in the discriminant function analysis as significantly contributing to AN clusters. Paper 6 found no evidence to support the existence of a gross planning impairment in young people with AN, despite inefficiencies in planning noted in the adult literature (e.g., Zakzanis et al., 2010). Rather, the findings of Paper 6 in conjunction with other studies that have used traditional planning tasks (e.g., Alvarado-Sánchez, Silva-Gutiérrez, & Salvador-Cruz, 2009; Dahlgren et al., 2013; Fowler et al., 2006; C. Gillberg et al., 2010) suggest the existence of subtle, such as faster initiation times, rather than gross planning differences.

Another discrepant finding between this thesis and the research literature concerns verbal fluency, in that Lena et al. (2004) and Zakzanis et al. (2010) have suggested poor verbal fluency in those with AN. Contrarily, in-line with a meta-analysis of verbal fluency in AN (Stedal, Frampton, Landro, & Lask, 2012), those in AN Cluster 3 were distinguished by strong verbal skills (Paper 4). It should be noted that this cluster accounted for 48% of the AN group. Verbal fluency in the remaining clusters was in the average range relative to population norms. Strong verbal fluency, verbal flexibility and inhibition (interestingly the inhibition task Colour-Word Interference requires a

verbal output) were distinguishing characteristics as seen from the discriminant function analysis (Paper 4).

Considerations for the field of neuropsychology in AN

There are a number of themes that should be discussed when considering the neuropsychology of AN, particularly early onset AN. These may hold possible reasons which may account for the differences in findings between this thesis and previous reviews in the field of AN.

Developmental trajectory.

Research in developmental neuropsychology supports the notion of performance differences across age groups (P. Anderson, 2002; V. Anderson, 2001; V. Anderson et al., 2001; Brocki & Bohlin, 2004; Giedd et al., 1999; Klimkeit, Mattingley, Sheppard, Farrow, & Bradshaw, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004). For example executive functioning is not a unitary concept, but can be divided into distinct categories that differ by cognitive skill, trajectory and maturation rate. These varying patterns are highly correlated with specific stages in neural development. Neuro-imaging studies have shown age-related changes in deep structures such as the amygdala and hippocampus (Hu, Pruessner, Coupe, & Collins, 2013), and tissue and tract volume (Lebel et al., 2012). Research by McGivern, Andersen, Byrd, Mutter, and Reilly (2002) has shown a non-linear decrease in frontal lobe grey matter during puberty that has been linked to the non-linear improvement seen in executive functioning tasks across age groups. Blakemore and Choudhury (2006) have highlighted MRI studies' identification

of changes in the prefrontal cortex during adolescence and suggested that these are responsible for the development of executive functions throughout this period. These developmental changes are in line with a longitudinal study that showed activity in most areas decreases with age, except in the frontal lobes (Durstun et al., 2006). This suggests that maturation of the frontal lobes is not complete until early adulthood (Gogtay et al., 2004) and that executive functions develop in parallel with the biological maturation process.

As highlighted in the discussion of Paper 5, it is of utmost importance to establish the *expected* levels of neuropsychological performance, particularly when assessing young children and adolescences, a period of both synaptogenesis and development of greater cognitive capacity. If test performance is compared to an inappropriate reference, be it norms or control data, there is a danger that performance maybe rated as “weak” rather than being recognised as developmentally appropriate. Zelazo and Muller (2011) highlight the importance of understanding typical development of the constructs of neuropsychological functioning in order to be able to determine what ‘atypical’ development may look like.

Paper 5 discusses that in the absence of age appropriate norms for functions such as central coherence, caution must be taken when interpreting performance data in young individuals with AN. A specific example of this is the application of adult assessment procedures to child performance. Central coherence is assessed using the Central Coherence Index (CCI) on the RCFT. This is partly based upon the degree of fragmentation of global

elements. An individual will receive a higher score for starting the figure with more global elements. Since it is the first third of completed elements that are scored, any fragmentation of these elements will result in a lower score. In adult populations, the CCI has been shown to discriminate between healthy controls and patients with AN. However, when investigating visuo-spatial constructional ability in a young population, assessments based on fragmentation of selected elements may not be sufficient to detect subtle differences (Akshoomoff & Stiles, 1995b). This method places greater emphasis on only a few elements as opposed to describing the method used to construct the whole figure. A more reliable assessment might include a child specific scoring systems such as the Boston Qualitative Scoring System (Stern et al., 1994), Organisational Strategy Score (P. Anderson, Anderson, & Garth, 2001) or the Developmental Scoring System (Bernstein & Waber 1996).

Not only should we recognise the importance of expected levels of performance and reliable assessment, but also an understanding of how trajectories differ, both between-functions and within-function. Levin et al. (1991) and Williams, Ponesse, Schachar, Logan, and Tannock (1999) suggest that whilst there is a developmental component to inhibition, by 12 years of age this cognitive function has reached relative maturity. Liston et al. (2006) found that myelination of projections between the prefrontal cortex and the striatum increased with age and were correlated with performance on a Go-No-Go task. This suggests that increasing efficiency of fronto-striatal connections may underlie the maturation of inhibitory control mechanisms.

In terms of organisational strategy, there is a developmental trend evident from 6 years of age that reaches approximate adult levels of performance by 12 years. However, several studies suggest further refinement of organisational strategies continues into middle and late adolescence (Akshoomoff & Stiles, 1995a; P. Anderson et al., 2001; Karapetsas & Kantas, 1991; Kirk, 1985; Waber & Holmes, 1985).

As such, whilst in early childhood improvements in neuropsychological functions may be rapid, by adolescence the changes in behavioural performance are merely refinements in speed and accuracy (Best & Miller, 2010). A more thorough knowledge of normative performance, between and within functions, that spans across childhood, middle and late adolescences is needed.

Effects of starvation on neuropsychological functioning.

The average adult human brain weighs approximately 1.4 kilograms, only 2 percent of our total body weight, yet it demands 20 percent of our resting metabolic rate (McKenna, Gruetter, Sonnewald, Waagepetersen, & Schousboe, 2006, p.532). This equates to approximately two thirds (between 300 and 600 calories) of the total daily glucose intake. The question of whether neuropsychological impairments in AN are a result of starvation or low body weight has yet to be answered, as the literature pertaining to this is equivocal.

Pendleton Jones, Duncan, Brouwers, and Mirsky (1991) assessed currently ill and recovered patients with AN, normal weight bulimia nervosa patients and healthy controls. An extensive neuropsychological battery was administered which assessed the domains of vigilance, executive functioning, verbal ability, memory and visuo-spatial processing. In all domains except vigilance, weight recovered patients performed intermediately between currently ill patients and controls. However, correction for multiple testing was not conducted. Tchanturia et al. (2004); Tchanturia et al. (2012); and Tchanturia et al. (2011) similarly found higher rates of set-shifting difficulties in those currently ill with AN compared to controls, as well as mixed finding of intermediate performance by recovered patients between currently ill and healthy controls. Such studies may highlight the role of malnutrition in neurocognitive functioning.

If impairments in this disorder were due to malnutrition and starvation, then theoretically one might assume that cognition would improve following weight gain. There is general consensus that the domain of attention improves with weight gain, which suggests a state related dysfunction (Bradley et al., 1997; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996; Lauer, Gorzewski, Gerlinghoff, Backmund, & Zihl, 1999; Mikos et al., 2008; Szmukler et al., 1992). Set-shifting and detail-focused/global integration difficulties persist that may indicate trait characteristics (I. C. Gillberg, Gillberg, Råstam, & Johansson, 1996; I. C. Gillberg, Råstam, Wentz, & Gillberg, 2007; Harrison, Tchanturia, & Treasure, 2011; Lopez, Tchanturia, Stahl, & Treasure, 2009; Tchanturia et al., 2012; Tchanturia et al., 2011; Tchanturia, Morris,

Surguladze, & Treasure, 2002). There are mixed findings concerning improvement of visuo-spatial processing skills, planning, inhibition, psychomotor functioning and learning (Green, Elliman, Wakeling, & Rogers, 1996; Grunwald et al., 2001; Kingston et al., 1996; Rastam, Gillberg, & Gillberg, 1995).

In contrast to the adult literature above, far fewer follow-up studies of cognitive functions in children and adolescents with AN have been conducted. There appears to be mixed evidence of improved cognitive performance following weight gain. Hatch et al. (2010) found significantly poorer performance in AN compared to controls in motor speed at baseline which normalise with weight gain. Buhren et al. (2012) showed an increased reaction time when engaging in set-shifting tasks and a reduced error rate across time. Kjaersdam Telleus et al. (2016) reported on a matched case-control longitudinal study that tracked cognitive development over one year. Generally no significant differences in the change of cognitive functions were found between those with AN and HCs. However, motor speed was one exception, with a greater improvement in change found in the patients with AN than in the HCs and reached HC levels at follow-up.

The effect of the nadir (lowest lifetime) BMI on cognitive functioning in eating disorders remains unclear. Whilst this factor has been implicated in the enduring decrease of cerebral white and gray matter in patients recovered from eating disorders (Joos et al., 2011; Titova, Hjorth, Schioth, & Brooks, 2013), studies suggest nadir BMI does not affect performance in central

coherence (Roberts, Tchanturia, & Treasure, 2013; Tenconi et al., 2010) or set-shifting (Tenconi et al., 2010). Weider, Indredavik, Lydersen, and Hestad (2014) reported nadir BMI as a powerful mediator in BN and AN. The authors suggest that an extremely low BMI may lead to a longer-lasting reduction in cognitive functioning or patients with premorbid cognitive difficulties develop a more severe ED.

These findings suggest that neuropsychological weaknesses, i.e., set-shifting and weak central coherence, can pre-exist AN development, and may not simply be the consequence of the disease itself (Nunn, Frampton, Gordon, & Lask, 2008). In evaluating the state vs. trait literature, methodological differences should be kept in mind. Studies using a between groups design may have limited inferential basis to explore the state vs. trait nature relative to a repeated measures design or those that incorporate both in a mixed design.

Early vs. later onset.

It is evident that the majority of diagnosed cases of AN receiving treatment are between 15 and 35 years of age (Bryant-Waugh & Lask, 2013). Illness onset may coincide with critical developmental phases such as puberty, thus this may have an influence on the development, course and outcome of the illness compared to those who develop the disorder later in life. Efforts to define what constitutes early onset remains unclear. For instance, 'early onset' has been defined as onset under the age of 18 years (Eisler et al., 1997), under 14 years (Bryant-Waugh & Lask, 2013; Matsumoto

et al., 2001) or in relation to early vs. late pubertal development/status (Arnow, Sanders, & Steiner, 1999; Cooper, Watkins, Bryant-Waugh, & Lask, 2002; Russell, 1985).

Early onset AN may have severe consequences given its occurrence in a highly sensitive developmental phase. During this time the brain is in a critical developmental phase with decreasing gray matter volume and increasing white matter volume due to synaptic pruning and myelination (Giedd et al., 1999). The effects of prolonged malnutrition and low weight may lead to partly irreversible changes in the developing brain (Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012).

Early onset studies into neurocognitive functioning have been relatively scarce, thus it is difficult to compare and establish whether the findings from our younger sample replicate those in the literature, i.e. the robustness of our findings. The age range in Paper 4 was 9 to 18 years of age thus the sample could potentially be classified as early onset if using less stringent criteria of Eisler et al. (1997). However, caution must be taken since the length and onset of illness were unknown. Paper 5 sought to compare visuo-spatial memory findings to studies which have used a similar age group. To our knowledge, only one study has exclusively focused on children and adolescents- Lask et al. (2005), which reported impairments in visuo-spatial memory and ability. Paper 5 did find low average performance in the group with AN, however this did not differ from age matched controls.

The studies in this thesis are unique in that they are the first to investigate the neuropsychological profile of AN, as well as discrete functions, in young individuals with AN. Despite the inconsistent definitions, the benefit of focusing on early onset AN is that results from such studies have the potential to inform early detection and targeted intervention strategies, for instance as already developed in the field of depression (Lewinsohn, Solomon, Seeley, & Zeiss, 2000).

Treatment of AN

Anorexia nervosa is associated with the highest rate of mortality amongst all mental health disorders (Harris & Barraclough, 1998). Arcelus, Mitchell, Wales, and Nielsen (2011) report a mortality rate of 5.1 deaths per 1000 person-years and the standardised mortality rate of 5.9 with a mean follow-up period of 14.2 years. The majority of deaths are a direct consequence of starvation-related medical complications, however one in five deaths are a result of suicide (Smink, van Hoeken, & Hoek, 2012). The need for effective treatments is imperative and there remains much scope for prognostic improvement. Research indicates that approximately 50% fully recover from AN, with the remainder chronically ill or partially improved (Berkman, Lohr, & Bulik, 2007); long term follow studies describe two broad categories of outcome, either a good outcome or chronic course with a high risk of premature death (Steinhausen, 2002; Zipfel, Lowe, Reas, Deter, & Herzog, 2000). Better outcomes are associated with illness onset before 18 years of age (compared to later onset), however pre-pubertal onset confers the worst outcome (Herpertz-Dahlmann, 2015). Hay, Touyz, and Sud (2012)

report there is a critical window for effective intervention in the early stages of illness (i.e., duration of <3 years) beyond which full recovery becomes much more difficult to achieve. Within adult patients with full syndrome AN, time to complete remission is between 5 and 6 years (Herzog, Schellberg, & Deter, 1997). Hence, adult onset AN has been described as “one of the most difficult psychiatric disorders to treat” (Halmi et al., 2005).

Treatment of AN is complex as it must address both the physical (e.g., weight gain, reducing risk of physical complications) and psychological aspects of the disorder (e.g., body image issues associated with emotional disturbance, rigid thinking, disordered cognitions, maladaptive behaviours). Historically comprehensive reviews have assessed the efficacy of psychological therapies for AN and have concluded there is insufficient evidence to support one treatment over another (Hay et al., 2012; Watson & Bulik, 2013). More recently, guidelines support the use of cognitive behavioural therapy (CBT) across a range of eating disorders in adults in the short and long term or systemic based therapy in young people with AN (National Institute of Clinical Excellence, 2017). Linardon, Wade, de la Piedad Garcia, and Brennan (2017) report equal efficacy between CBT and interpersonal psychotherapy (IPT) at long term follow-up periods. Hilbert, Hoek, and Schmidt (2017) compared international treatment guidelines for eating disorders and noted that of eight available guidelines, six recommended CBT for adults with AN whilst family-based therapy, particularly for adolescents, was recommended by six guidelines.

A neuropsychologically informed approach to treatment- Cognitive remediation therapy (CRT).

The neuropsychological inefficiencies reported in AN are not the focus of current evidence based treatments. For example, CBT targets normalising eating patterns and addressing cognitive distortions, whilst family based treatment focuses of parental blame reduction, building helpful dialogue between family members and transitioning eating and weight control back to the adolescent in an age appropriate manner. Since treatment refusal and dropout rates are high and relapse is common (Keel & Brown, 2010), it is important to continue developing adjunctive or alternative treatments that target these underlying neuropsychological inefficiencies.

CRT was initially developed for patients with brain lesions and brain injuries. More recently it has been used as an effective treatment for psychosis and attention deficit disorder (Tchanturia, Lloyd, & Lang, 2013). Tchanturia and Hambrook (2009) developed its use for AN as a way of improving neurocognitive abilities such as central coherence and set-shifting skills. The therapy consists of simple cognitive exercises designed to develop a more flexible and holistic thinking style, e.g., thinking about *thinking*. The process of reflecting upon their own cognitive style increases self-awareness and encourages more adaptive thinking styles that can be generalised to real-life situations and everyday behaviours. Typically CRT is used as an adjunctive intervention alongside evidence-based treatment with the intention

of reducing treatment drop-out and improving cognitive functioning (Danner, Dingemans, & Steinglass, 2015; Tchanturia et al., 2013).

CRT in adults with AN.

Reviews by Dahlgren and Rø (2014) included 21 studies and Tchanturia, Lounes, and Holttum (2014) included 15 studies that spanned a range of study designs. Overall, single case studies and case series supported the feasibility of CRT across ages, illness severity, current treatment engagements and when delivered in individual and group formats. Both reviews included four RCTs (Brockmeyer et al., 2014; Dingemans et al., 2014; Lock et al., 2013; Steinglass et al., 2014) that used predominantly adult samples. Brockmeyer et al. (2014) and Lock et al. (2013) demonstrated efficiency in improving specific neurocognitive functions whilst Dingemans et al. (2014) found CRT was associated with significant improvements in quality of life post-CRT and ED symptoms at follow-up. Furthermore, Lock et al. (2013) reported reduced attrition and improved concurrent treatment in the CRT group.

CRT in children and adolescents with AN.

Whilst research focused on CRT with children and adolescents is behind adult focused research, CRT protocols have been developed for use with adolescents in a variety of clinical settings (Fitzpatrick & Lock, 2015; Maiden, Baker, Espie, Simic, & Tchanturia, 2014). Dahlgren and Rø (2014) concluded that adolescent CRT case studies and series supported the feasibility and acceptability of the intervention although the lack of RCTs in

younger AN populations makes it difficult to comment on the intervention's potential in terms of efficacy. The authors also draw attention to research that has not found neuropsychological deficits in younger AN samples that have been found in adult populations, thus to consider components other than neuropsychological performance when assessing the effect of CRT in younger populations such as attrition reduction, enhancing the effectiveness of concurrent treatments or broader benefits that might manifest in day-to-day life such as metacognitive abilities.

Tchanturia, Giombini, Leppanen, and Kinnaird (2017) reviewed studies on CRT for AN for young people that included nine case studies, case series and qualitative assessments. Meta-analyses found CRT to significantly improve central coherence and executive functioning as measured by the Behaviour Rating Inventory of Executive Function (BRIEF, Guy, Isquith, & Gioia, 2004), both of small effect sizes. However, CRT was not significantly beneficial on set-shifting performance. The authors concluded that CRT for young people with AN appeared to be less constant than for adults, in that set shifting and central coherence improvements were more widely documented and of larger effect sizes in adult based studies.

The future of CRT.

The Ravello Profile can play a role in future CRT research. For example, understanding the specific neurocognitive strengths and weaknesses of the patient can allow tailoring of CRT to specific domains, be that enhancing poor performance as well as building on current strengths.

Dingemans et al. (2014) showed that patients with poorer baseline set-shifting abilities benefited more from CRT. Utilizing a tailored approach is important in light of limited support for set-shifting difficulties in children and adolescents with AN compared to adult populations (Lang et al., 2014b; Westwood et al., 2016). Thus, it is important to explore whether CRT for children and adolescents with AN may have less utility than for adults or whether it can benefit by aiding the development of adaptive cognitive functioning. Furthermore, administration of lengthy neurocognitive assessment batteries may be problematic for busy clinicians and researchers. The findings from the Ravello Profile may help inform a Short Form and/or computer-based version of a neuropsychological assessment battery for use in AN. A possible avenue of research is described below under clinical and research implications.

The impact of CRT on concurrent treatments is worth pursuing. Conventional talking therapies require the patient to engage in complex cognitive processes, yet individuals with AN can exhibit several cognitive processing inefficiencies therefore the ability to engage in such treatments may be compromised (Tchanturia & Lang, 2015). For example, rigidity in thinking may hinder giving up specific food and eating rules. Using a therapy that does not directly target eating cognitions and behaviours in the early stages of the treatment process might aid therapeutic engagement by reducing drop out and developing alternative thinking styles which in turn allow the patient to access other evidence-based approaches that directly address eating disorder symptoms. This is particularly significant as early

engagement in treatment is associated with better outcomes (Tchanturia et al., 2013; Tchanturia et al., 2014).

Reviews of CRT in the treatment of AN have highlighted a number of limitations such as research often conducted in inpatient populations, with small samples and limited statistical power, which severely limits the generalisability of the results. Despite these limitations, preliminary evidence using CRT for the treatment of AN appears promising, in particular having good feasibility in younger populations. CRT is accepted by both patients and clinicians (Pretorius et al., 2012; Tchanturia et al., 2017), for example inpatient adolescents with AN found a group-based CRT program to be fun, playful and engaging (Wood, Al-Khairulla, & Lask, 2011). Alongside benefits in attrition and improved neurocognitive performance, there is evidence that CRT can decrease perfectionist tendencies (Pitt, Lewis, Morgan, & Woodward, 2010), a core feature of AN. Perfectionism has been identified in the transdiagnostic cognitive behavioural model of eating disorders as one of four key maintaining mechanisms that interacts with other associated psychopathology (Fairburn, Cooper, & Shafran, 2003). Future RCT research into the efficacy of CRT in younger populations is warranted.

Clinical and research implications

The Research Domain Criteria (RDoC) Project (US National Institute of Mental Health, 2010) describes a framework for studying mental disorders that integrates multiple levels of information (from genomics to self-report) to better understand functions that underlie human behaviour. RDoC specifies

five domains or psychological constructs that are relevant to human behaviour: negative valence systems, positive valence systems, cognitive systems, social processes and arousal and regulatory systems. Methods to investigate these domains are termed “units of analysis” that are defined under eight classes: genetic, molecular, cellular, neural circuits, physiology, behavioural (which includes neuropsychology), self-reports and paradigms.

Paper 1 proposed that with the advent of RDoC, future neuroscience models can be developed around a common framework which will help foster comparisons between them. Distinguishing features in specific classes (such as key neurotransmitters or neural circuits) should help in designing experimental tests to support or refute their role. Arguably, one of the major reasons why eating disorders (especially AN) have proven so difficult to treat is that we have lacked a coherent understanding of what causes them. By testing and refining models incorporating the range of classes defined in RDoC, we should improve our ability to design and target specific treatments.

With regard to future neuropsychological assessment research, a “profile” approach that employs paper and pencil tasks may seem outdated when compared to modern, computer based assessments that are data rich and often able to auto-score and collate. However, there is a danger that such methods lack population based norms and rely on comparison to control data. As pointed out by Reville et al. (2016), there is already an abundance of studies, often of small sample sizes, that emphasis significant differences between patient and control participants without correcting for multiple

comparisons leading to increased risk of false-positive errors. Traditional approaches to neuropsychological testing typically measure performance across a large battery of tests across a spectrum of functions. This exploratory approach can inform empirically based theory building, and when triangulated against other research methods as emphasised by RDoC, the field of AN can benefit from the reduced likelihood of false positives.

Wildes and Marcus (2015) reviewed RDoC-informed eating disorder studies and noted that few studies have utilised the framework, instead categorising samples according to DSM or ICD diagnostic criteria. Wildes and Marcus called for future studies to consider using the RDoC framework, such as classifying groups based on response to a behavioural task, or reporting outcomes that represent multiple units of analysis (e.g., circuits, physiology, self-reports) as well considering potential interactions among various RDoC domains and constructs (e.g., positive valence and cognitive control systems). Ultimately, interventions, both new and existing would benefit from targeting specific disease mechanisms. RDoC can help in this endeavour of improving treatments for mental disorders by matching patients to interventions designed to target the pathophysiological mechanisms that underlie symptom expression. Based on the neuropsychological constructs within RDoC, Lutter, Croghan, and Cui (2016) propose a comprehensive and systematic basis for the investigation of the neural substrates underlying the biological predisposition to eating disorders. By reporting on studies that demonstrate deficits in patients with eating disorders across the RDoC domains, the authors suggest a set of behavioural tasks that reflect those deficits and

allows comprehensive examination of the function of neural circuits relevant to the development of eating disorders. A key to developing effective treatments for AN might lie in a clearer understanding of how AN symptoms and behaviours are encoded in neural circuits.

Several clinical and research implications emerge from this thesis. These are discussed in turn:

- 1) The creation of a standardised neuropsychological assessment battery will help improve comparability between studies and allow generalisation of findings. To date, the heterogeneity of neuropsychological tests used has made this very difficult. It may be beneficial for the field of AN to consider the development and research of Short Forms and/or computer-delivered neuropsychological assessment batteries for use in AN. A possible avenue to explore would be the development of a Ravello Profile Short Form based on the discriminant function analysis from Paper 4. The two discriminant functions that defined AN cluster membership were Function 1 “visuo-spatial processing” and Function 2 “verbal fluency, verbal flexibility and inhibition”. Roberts, Barthel, Lopez, Tchanturia, and Treasure (2011) developed the Detail and Flexibility Questionnaire (DFlex) for use in AN that measured two aspects of neurocognitive functioning- attention to detail and cognitive rigidity. Arguably there is potential overlap between the discriminant function analysis and the DFlex in that Function 1 corresponds to attention to detail whilst Function 2 corresponds to

cognitive rigidity. A study using both the Ravello Profile and DFlex may a) offer a potential concurrent validity check to support the external validity of the clustering approach and b) indicate which neuropsychological tasks from Functions 1 and 2 could make up a Ravello Profile Short Form.

- 2) The core cognitions and behaviours in AN can be conceptualised in terms of neuropsychological dysfunction. For example, executive functioning deficits such as poor problem solving ability may be implicated in a high need for control; poor information processing style in the form of weak central coherence can be considered in terms of perfectionism and set shifting impairments may be closely linked to cognitive and behavioural inflexibility. Impairment in visuo-spatial ability may be implicated in body size estimation errors.
- 3) Dysfunctional neuropsychological performance has been significantly associated with a poorer outcome (Hamsher, Halmi, & Benton, 1981), thus neuropsychological markers may have potential to inform detection and intervention. Targeting specific impairments via CRT may have the potential to improve outcome, for example patients with weak central coherence may benefit by being taught skills to help think in a more global or holistic manner. The current CRT evidence base suggests good feasibility in younger populations. Using CRT as an adjunct to evidence based therapies such as CBT can aid therapeutic engagement (as evidenced by lower attrition rates) and enhance the effectiveness of concurrent treatments.

- 4) Neuropsychological profiling has the potential to inform research into the underlying neurobiology of anorexia nervosa, associated risk factors, as well as identify both shared and illness-specific phenotypes. The underlying heterogeneity found in the profiles may suggest distinct pathophysiologies.
- 5) It will now be possible to investigate the associations between neuropsychological clusters with factors such as outcome, e.g., whether neuropsychological profiling can be used with targeted interventions such as CRT. Such research could elucidate on whether there are different illness trajectories, or whether specific clusters are linked with poorer prognosis.
- 6) Paper 4 raises an important point regarding the inconsistent use of terminology used in the field of AN, i.e., deficits, impairments, weaknesses and inefficiencies. Paper 3 and 4 used a ranked system of severity based on standard deviations from the population mean (where population norms exist). Some studies have labelled weaker performance by patients with AN as deficits or impairments, yet when compared to population norms, such performance is within the average range. The field would benefit from employing consistent terminology in describing the neuropsychological characteristics of this patient population. Another recommendation is that case-control studies should present their findings with reference to population norms, be it scaled scores, percentiles, or Z score conversion, to give insight into the prevalence of neuropsychological dysfunction.

- 7) Paper 5 and 6 highlight the value of understanding the developmental trajectory of neuropsychological processes. Simply applying adult tests to young children without consideration for how skills develop or the appropriateness/sensitivity of tests may seriously invalidate the conclusions drawn. Further to this, it is recommended that for functions where no normative data exists, such as central coherence, that we have a deeper, more thorough knowledge of the developmental trajectory and its assessment in young people in the general population before drawing conclusions about its role in psychiatric disorders.
- 8) The debate on whether neuropsychological impairments in AN are a result of starvation or low body weight still continues. This is a problematic area in terms of research due to the ethical implications of subjecting otherwise healthy subjects to a period of starvation. Related to this is the question of whether dysfunction is state vs. trait. Despite a number of longitudinal design studies in this area, time intervals between assessments may not be long enough, as starvation effects may take longer to recover from than longitudinal study designs allowed for (Lena et al., 2004).
- 9) For functions such as inhibition and set-shifting, perhaps these should not be viewed as discrete entities but viewed as related functions in line with contemporary executive functioning theories. Studies focusing on single domains maybe inherently flawed, in that conclusions based on such studies will always miss or never truly understand the role of neuropsychological functioning in AN. For instance, one would not focus on a single gene or neurotransmitter in trying to understand the

role of genetics or neurochemistry in a given disorder. Interactions are just as important as unique functioning. Such studies are necessary but not sufficient in explaining how neuropsychological factors play a role in the development and maintenance of AN.

- 10) The findings of systematic reviews in the field of AN suggest that future studies should address differences between input modality of the cognitive tasks (i.e. visual vs. verbal), the impact of co-morbidity, the contributory role of malnutrition and also take into account multiple measures (i.e. time vs. errors) from a single cognitive task, in that the averaging of scores may mask subtle but important findings. Lena et al. (2004) note that for pre-post treatment studies investigating cognitive functioning, time intervals between assessments may not have been long enough, as starvation effects may take longer to recover from than longitudinal study designs allowed for. Added to this confound were mixed samples of subtypes and ED diagnoses which again may be masking subtle dependent effects. As the literature stands, it is unknown whether recovery occurs in full and whether improved functioning is possible across all domains.

Conclusion

In order to better understand the processes that may underlie the distorted thinking seen in AN and address the challenges and inconsistencies within this field, this thesis aimed to explore neuropsychological dysfunction in children and adolescents with AN through neuropsychological profiling to identify distinct profiles and their association with specific clinical

characteristics. In addition, two specific domains of neuropsychological functioning were further explored- visuo-processing skills and planning ability. In summary, this thesis highlighted a critical volume of conceptual neuroscience studies in AN. Perhaps now is the time to integrate and refine our understanding by falsifying existing models (rather than creating more novel ones) and targeting specific components of AN for treatment as guided by a framework such as RDoC. It is hoped the development of the Ravello Profile neuropsychological battery proves beneficial for researchers and clinicians in overcoming the identified challenges within the field of AN. This thesis provides evidence of subtle neuropsychological heterogeneity in children and adolescents with AN. While these findings require replication, it is exciting to consider the prospect that future neuropsychological profiling studies may have the potential to offer an insight into the underlying neurobiology of AN, to guide treatment strategies and to inform future research. Ultimately, the purpose of this research endeavour has been to contribute to improving the outcomes for patients suffering from this poorly understood and difficult to treat disorder.

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Appendix 1: Quality appraisals of thesis papers

Paper 1: Conceptual models critical appraisal.

Based on the CASP systematic review checklist (Critical Appraisal Skills Programme, 2018a), Paper 1 met 9 out of 9 criteria. However, a flaw that was not identified by the appraisal tool was the lack of reported methodology since this paper was published as a non-peer reviewed book chapter (had this been published in a journal then methodology would have been required). This is considered a flaw as there is no way for readers to replicate the review or assess appropriate of databases searched, search terms or inclusion/exclusion criteria.

Paper 2: Ravello development paper critical appraisal.

Based on the CASP checklist for qualitative research (Critical Appraisal Skills Programme, 2018b), Paper 2 met four out of nine criteria. Details of specific weaknesses were as follows:

Q1. Was there a clear statement of the aims of the research?

The background and rationale are reported, although aims are not explicitly stated.

Q4. Was the recruitment strategy appropriate to the aims of the research?

Not clear. The working group were members of a neuroscience Special Interest Group which would suggest an appropriate knowledge base for the aims of this study. However, how the

working group members were selected, who they were or level of expertise were not reported.

Q5. Was the data collected in a way that addressed the research issue?

Not clear. The setting for the data collection was appropriate. Given that discussions were had at a series of conferences and meetings, a focus group format was adopted by the working group, although this is not explicitly stated. A Delphic approach to the battery creation was used, however details of the exact procedure were not reported- selection of panellists, specifying the number of rounds and the objectives of each round, how the data (opinions) were recorded and ranked.

Q6. Has the relationship between researcher and participants been adequately considered?

No details of the relationship between the researcher and working group were reported

Q8. Was the data analysis sufficiently rigorous?

Data analysis procedure was not reported. It is unknown how the data were analysed, e.g., whether agreement must meet a specified cut off, decided a priori.

Paper 3- Case series critical appraisal.

Based on the Quality Assessment Checklist (Moga et al., 2012), the case series met 9 out of 14 criteria. Specific weak points of the case series were as follows:

Q4. Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate? The following four criteria were regarded as important: 1) Specific distinctive features of the neuropsychological profile, i.e., a score \pm two standard deviations from the population mean, 2) diagnosed with anorexia nervosa, 3) under the age of 18 years, 4) female

The original inclusion criteria were not adequately stated, other than cases being chosen due to their distinctive neuropsychological profile to illustrate a range of profiles. The specific distinguishing neuropsychological features are not specified. It is not explicitly stated a priori that patients must meet a specific diagnosis, age or gender.

Q5. Were participants recruited consecutively?

No. Recruitment was based on having a distinctive profile. No other details were given.

Q6: Did participants enter the study at a similar point in the disease? The following four criteria were regarded as important: 1) Length of illness prior to neuropsychological assessment, 2) illness severity, 3) co-morbidity, 4) weight status.

Mainly yes, thus a partial weakness. All participants were ill at the time of recruitment with a clear description of clinical status- symptom severity, weight status and co-morbidity. Length of illness was not reported. However, this was mentioned in the limitations. Severity of symptoms varies from low to high (Global EDE range 0.76 to 5.70) suggesting heterogeneity of the clinical sample. Weight status was low relative to their age (all below the 12th percentile). Diagnostic subtype was unknown as well, this was mentioned in the limitations.

Q12. Were the statistical tests used to assess the relevant outcomes appropriate?

No statistics were reported, results were descriptive. The authors could have stated if the sample mean was significantly different from population mean. However the value of this would be questionable given the small sample and the fact cases were specifically selected.

Q16. Are adverse events reported?

There was no statement about adverse events.

Q18. Are both competing interest and source of support for the study reported?

No details were provided.

Paper 4: Distinct neuropsychological profiles in anorexia nervosa critical appraisal.

Based on the STROBE (Vandenbroucke et al., 2007), 16 out of the 22 criteria were met. Below are the specific weaknesses:

Q1: Title and abstract. (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found.

a) Study design was not specifically mentioned in the title or abstract.

Q4: Study design. Present key elements of study design early in the paper.

There is no specific mention that this was a cross-sectional study.

Q16: Main results. (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.

a) Between cluster differences: Main effect of clusters did not control for IQ.

Q17. Other analyses. Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.

No sensitivity analysis of effect of missing data imputation.

Q21: Generalisability. Discuss the generalisability (external validity) of the study results

Given the high degree of co-morbidity in the sample, findings cannot be generalised to those with AN only, but rather with AN and a high degree of co-morbid depression, anxiety and OC symptoms.

Findings are generalisable to young people with AN between the ages of 9 to 18 years. However, this may not be the case for younger (< 9 years) or older (> 19 years) cases with AN.

Due to the large number of collaborator sites, the authors believe that those in the sample would be generally representative of the disorder. If cases had been recruited from a single site, sample bias may have occurred.

Paper 5: Central coherence, organisational strategy and visuo-spatial memory in children and adolescents with anorexia nervosa critical appraisal.

Based on the STROBE (Vandenbroucke et al., 2007), 17 out of the 22 criteria were met. Below are the specific weaknesses:

Q1: Title and abstract. (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found.

a) Study design was not specifically mentioned in the title or abstract.

Q12: Statistical methods. (a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—If applicable, explain how loss to follow-up was addressed. Case-control study—If applicable, explain how matching of cases and controls was addressed. Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses

c) No information on missing data was provided. Table 3 and 4 do show there were missing data for some variables.

*d) Matched analyses were not conducted, i.e., paired *t* tests instead of independent sample *t* tests*

e) No sensitivity analyses for missing data were conducted.

Q14: Descriptive data. (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—Summarise follow-up time (e.g., average and total amount)

b) No information on missing data were provided. As stated for Q12c, missing data is evident from the numbers provided for each variable/group in Table 3 and 4.

Q17: Other analyses. Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.

No other analyses were conducted. No missing data analysis.

Q22: Funding. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

Funding information was not provided in this study.

Paper 6: Deconstructing planning ability critical appraisal.

Based on the STROBE (Vandenbroucke et al., 2007), 17 out of the 22 criteria were met. Below are the specific weaknesses:

Q1: Title and abstract. (a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.

a) Study design was not specifically mentioned in the title or abstract.

Q12: Statistical methods. (a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—If applicable, explain how loss to follow-up was addressed. Case-control study—If applicable, explain how matching of cases and controls was addressed. Cross-sectional study—If applicable, describe analytical

methods taking account of sampling strategy. (e) Describe any sensitivity analyses.

- c) No information on missing data was provided. Table 1 and 3 do show there were missing data for some variables.*
- d) Matched analyses were not conducted, i.e., paired t tests instead of independent sample t tests.*
- e) No sensitivity analyses conducted.*

Q17: Other analyses. Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.

No sensitivity analysis for missing data. Comorbidity was not controlled for due to small effect sizes. This should have been tested and reported though.

Q22: Funding. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

Funding information was not provided in this study.

Appendix 2: Vancouver Declarations by co-authors

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M. & Frampton, I. (2011). Conceptual Models. In Lask, B., & Frampton, I. (2011). Eating Disorders and the Brain. Chichester: Wiley-Blackwell.

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the data analysis.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the manuscript and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 21/08/18

Vancouver Declaration

Name: Dr Jennifer Davis

Rose, M., Davis, J., Frampton, I., & Lask, B. (2011). The Ravello Profile - development of a global standard neuropsychological assessment for young people with anorexia nervosa. *Clinical Psychology and Psychiatry*, 16(2), 195-202. DOI: 10.1177/1359104511401191

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the original conception of the paper and assisted in data collection, analysis and interpretation of the data.

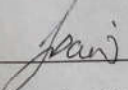
2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed:  _____

Date: 21st September 2018.

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M., Davis, J., Frampton, I., & Lask, B. (2011). The Ravello Profile - development of a global standard neuropsychological assessment for young people with anorexia nervosa. *Clinical Psychology and Psychiatry*, 16(2), 195-202. DOI: 10.1177/1359104511401191

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the original conception of the paper, data gathering and assisted in interpretation of the data.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 21/08/18

Vancouver Declaration

Name: Prof Bryan Lask

Rose, M., Davis, J., Frampton, I., & Lask, B. (2011). The Ravello Profile - development of a global standard neuropsychological assessment for young people with anorexia nervosa. *Clinical Psychology and Psychiatry*, 16(2), 195-202. DOI: 10.1177/1359104511401191

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I contributed to the original conception of the paper, data gathering and assisted in interpretation of the data.

2. My contribution to drafting the article or revising it critically for important intellectual content:

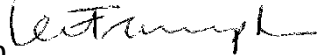
I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Bryan Lask

Signed: pp 

Date: 21/08/18

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M., Frampton, I., & Lask, B. (2012). A Case Series Investigating Distinct Neuropsychological Profiles in Children and Adolescents with Anorexia Nervosa. *European Eating Disorders Review*, 20(1), 32-38. DOI: 10.1002/erv.1095

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3. Approval of the version published:

I approved the version that is published.

Any comments:

Bryan Lask

Signed: pp 

Date: 21/08/18

Vancouver Declaration

Name: Dr Kristin Stedal

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. Archives of Clinical Neuropsychology, 31(8), 877-895. DOI: 10.1093/arclin/acw068

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2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 23 AUGUST 2018

Vancouver Declaration

Name: Marie-Claire Reville

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. Archives of Clinical Neuropsychology, 31(8), 877–895. DOI: 10.1093/arclin/acw068

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I contributed to the data analysis and interpretation.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed:



Date:

18/9/18

Vancouver Declaration

Name: Dr. phil. Betteke Maria van Noort

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. Archives of Clinical Neuropsychology, 31(8), 877–895. DOI: 10.1093/arclin/acw068

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3. Approval of the version published:

I approved the version that is published.

Any comments: /

Signed: 

Date: 23rd august 2018, Benin

Vancouver Declaration

Name: Dr. Viola Kappel

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. Archives of Clinical Neuropsychology, 31(8), 877-895. DOI: 10.1093/arclin/acw068

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I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: V. Kappel

Date: August 27th 2018

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. *Archives of Clinical Neuropsychology*, 31(8), 877–895. DOI: 10.1093/arclin/acw068

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I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 21/08/18

Vancouver Declaration

Name: Dr Beth Watkins

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. *Archives of Clinical Neuropsychology*, 31(8), 877–895. DOI: 10.1093/arclin/acw068

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I contributed to the original conception of the paper and interpretation of analyses.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: Beth Watkins

Date: 28/08/18

Vancouver Declaration

Name: Prof Bryan Lask

Rose, M., Stedal, K., Reville, MC., van Noort, B., Kappel, V., Frampton, I., Watkins, B. and Lask, B. (2016). Similarities and differences of neuropsychological profiles in children and adolescents with anorexia nervosa and healthy controls using cluster and discriminant function analyses. Archives of Clinical Neuropsychology, 31(8), 877–895. DOI: 10.1093/arclin/acw068

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3. Approval of the version published:

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Any comments:

Bryan Lask

Signed: pp 

Date: 21/08/18

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M., Frampton, I., & Lask, B. (2014). Central Coherence, Organisational Strategy and Visuo-Spatial Memory in Children and Adolescents with Anorexia Nervosa. *Applied Neuropsychology: Child*, 3(4), 284-96. DOI: 10.1080/21622965.2013.775064

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the conception of the paper.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 21/08/18

Vancouver Declaration

Name: Prof Bryan Lask

Rose, M., Frampton, I., & Lask, B. (2014). Central Coherence, Organisational Strategy and Visuo-Spatial Memory in Children and Adolescents with Anorexia Nervosa. *Applied Neuropsychology: Child*, 3(4), 284-96. DOI: 10.1080/21622965.2013.775064

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3. Approval of the version published:

I approved the version that is published.

Any comments:

Bryan Lask

Signed: pp 

Date: 21/08/18

Vancouver Declaration

Name: Marie-Claire Reville

Rose, M., Reville, MC., Iszatt, A., Levinson, S., Frampton, I. and Lask, B. (2016).
Deconstructing planning ability in children and adolescents with anorexia
nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI:
10.1080/21622965.2016.1172312

1. My contribution to conception and design, or development and analysis of a
theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the interpretation of the data.


2. My contribution to drafting the article or revising it critically for important
intellectual content:

*I contributed to initial drafts of the article and submitted critical reviews to the
first author.*

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 18/9/18

Vancouver Declaration

Name: Amber Iszatt

Rose, M., Reville, MC., Iszatt, A., Levinson, S., Frampton, I. and Lask, B. (2016). Deconstructing planning ability in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI: 10.1080/21622965.2016.1172312

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to the data analysis.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: A. Iszatt

Date: 22/08/18

Vancouver Declaration

Name: Simon Levinson

Rose, M., Reville, MC., Iszatt, A., Levinson, S., Frampton, I. and Lask, B. (2016). Deconstructing planning ability in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI: 10.1080/21622965.2016.1172312

1. My contribution to conception and design, or development and analysis of a theoretical model, or acquisition of data, or analysis and interpretation of data:

I contributed to conception of the paper, data analysis and interpretation of the data.

2. My contribution to drafting the article or revising it critically for important intellectual content:

I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 23/08/2018

Vancouver Declaration

Name: Dr Ian Frampton

Rose, M., Reville, MC., Iszatt, A., Levinson, S., Frampton, I. and Lask, B. (2016). Deconstructing planning ability in children and adolescents with anorexia nervosa. *Applied Neuropsychology: Child*, 6, 297-304. DOI: 10.1080/21622965.2016.1172312

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I contributed to initial drafts of the article and submitted critical reviews to the first author.

3. Approval of the version published:

I approved the version that is published.

Any comments:

Signed: 

Date: 21/08/18

Vancouver Declaration

Name: Prof Bryan Lask

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Date: 21/08/18